



Origin and Evolution of the Neuroendocrine Control of Reproduction in Vertebrates, with Special Focus on Genome and Gene Duplications

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Sylvie Dufour, Bruno Quérat, Hervé Tostivint, Catherine Pasqualini, Hubert Vaudry, et al.. Origin and Evolution of the Neuroendocrine Control of Reproduction in Vertebrates, with Special Focus on Genome and Gene Duplications. *Physiological Reviews*, 2020, 100 (2), pp.869-943. 10.1152/physrev.00009.2019 . hal-02383899

HAL Id: hal-02383899

<https://hal.science/hal-02383899>

Submitted on 15 Nov 2022

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Origin and evolution of the neuroendocrine control of reproduction in vertebrates, with special focus on genome and gene duplications

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Abstract

In human, as in the other mammals, the neuroendocrine control of reproduction is ensured by the brain-pituitary gonadotropic axis. Multiple internal and environmental cues are integrated *via* brain neuronal networks, ultimately leading to the modulation of the activity of gonadotropin-releasing hormone (GnRH) neurons. The decapeptide GnRH is released into the hypothalamic-hypophyseal portal blood system, and stimulates the production of pituitary glycoprotein hormones, the two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A novel actor, the neuropeptide kisspeptin (Kiss), acting upstream of GnRH, has attracted increasing attention in recent years. Other neuropeptides, such as gonadotropin-inhibiting hormone (GnIH) / RF-amide related peptide (RFRP), and other members of the RF-amide peptide superfamily, as well as various non-peptidic neuromediators such as dopamine and serotonin also provide a large panel of stimulatory or inhibitory regulators. This paper addresses the origin and evolution of the vertebrate gonadotropic axis. Brain-pituitary neuroendocrine axes are typical of vertebrates, the pituitary gland, mediator and amplifier of brain control on peripheral organs, being a vertebrate innovation. The paper reviews, from molecular and functional perspectives, the evolution across vertebrate radiation of some key-actors of the vertebrate neuroendocrine control of reproduction, and traces back their origin along the vertebrate lineage and in other metazoa before the emergence of vertebrates. A focus is given on how gene duplications, resulting from either local events or from whole genome duplication events (WGD), and followed by

paralogous gene loss or conservation, might have shaped the evolutionary scenarios of current families of key-actors of the gonadotropic axis.

1. Introduction

The neuroendocrine control of reproduction has been extensively investigated in mammals (for review: (370)). Two pituitary hormones, the gonadotropins, *i.e.* luteinizing hormone (LH) and follicle-stimulating hormone (FSH), are released in the general blood circulation and regulate gonad activity. The synthesis and release of gonadotropins is mainly controlled by a neuropeptide, gonadotropin-releasing hormone (GnRH), produced by hypothalamic neurosecretory neurons and released into the portal blood system connecting the median eminence to the adenohypophysis. GnRH neuron activity is itself regulated by various brain neuromediators, which allows the integration of multiple environmental and internal cues in the course of developmental or seasonal control of reproduction (Figure 1).

Other major physiological functions in mammals are similarly controlled by brain-pituitary-peripheral gland axes, such as the thyrotropic axis (brain-pituitary-thyroid) for development and metabolism, the somatotropic axis (brain-pituitary-liver) for body growth, the corticotropic axis (brain-pituitary-adrenal gland) for stress and metabolism. The pituitary gland and its role as a relay between the brain and peripheral glands or peripheral organs, is considered as an innovation of the vertebrate lineage (for review: (641, 738, 740)). The pituitary gland with its production of pituitary hormones under the control of brain neurohormones is a common feature to all vertebrates, even though some anatomical variations in the brain-pituitary relationships are observed. In mammals as in other tetrapods, hypophysiotropic neurons project to the median eminence and neurohormones are released into the pituitary portal system which irrigates the adenohypophysis, while, in teleost fishes, hypophysiotropic neurons directly project up to the adenohypophysis which exhibits a high

regionalization of pituitary cell types (231, 287). In cyclostomes (hagfish and lamprey), brain neuropeptides reach the adenohypophysis by diffusion from the third ventricle, which may represent the ancestral pattern of connection between the hypothalamus and the pituitary in vertebrates (for review: (738)).

We review here current information and hypotheses on the origin, conservation and variations of the key actors of the vertebrate brain-pituitary control of reproduction, with a special attention to the impact of gene and genome duplication events in the evolutionary scenario of their molecular families.

2. Looking for the origin and evolution of the neuroendocrine control of reproduction

2.1. Objectives

Comparative biologists have been investigating the control of reproduction as well as of other physiological functions in non-mammalian vertebrates and other metazoa. Comparative studies not only provided specific information on species of interest, but also led to major advances for basic research. A remarkable example concerns the “neurosecretion” process, *i.e.* the ability of certain neurons to synthesize and release hormones, a property exhibited for instance by GnRH neurons. Hypothalamic neurosecretory neurons were first described in 1928 in a teleost fish species, *Phoxinus laevis*, by Ernst Scharer (679), who established the concept of “neurosecretion”, a few years after the description by Carl Speidel (1919) (742) of some “glandular” neurons in the spinal cord of chondrichthyan fish, the skates (for reviews: (665, 678)). In the same line, the first RF-amide peptide, designated after the C-terminal arginine (R) and amidated phenylalanine (F) residues, has been isolated in 1977 from the ganglia of a mollusk, the Venus clam, *Macrocallista limbosa* (623). Since then, an increasing number of RF-amide peptides have been identified in all metazoa, constituting the RF-amide

199 superfamily and including some brain peptides involved in the neuroendocrine control of
200 reproduction in vertebrates (see section 5).

201 Comparative and evolutionary reproductive neuroendocrinology is arousing interest for
202 various disciplinary fields, thanks to the variety of biological models investigated and the
203 availability of tools such as genome sequences. There is an increasing attention to teleosts
204 (*e.g.* zebrafish) as vertebrate models for biomedical research, and an increasing diversity of
205 species investigated worldwide for their relevance to agriculture, aquaculture, conservation,
206 or environmental assessment. Comparative and evolutionary neuroendocrinology aims at
207 tracing back the roots and the evolution of the neuroendocrine systems, from molecular and
208 functional perspectives, and at inferring their roles in the evolution of metazoan species and
209 lifecycles. For agronomic sciences, it contributes to increase basic and applied knowledge for
210 sustainable control of reproductive cycles in captivity, for understanding domestication
211 processes, for diversifying cultured species such as in aquaculture, and promoting sustainable
212 agro/aqua-systems. For conservation biology, it provides new knowledge for understanding
213 the role of neuroendocrine systems in species adaptation and adaptability to environmental
214 factors, a crucial topic in the context of global, climatic and anthropogenic changes. In
215 biomedical sciences, comparative and evolutionary neuroendocrinology contributes to
216 innovative advances by providing alternative vertebrate models suitable for experimentation
217 such as zebrafish, by revealing the evolutionary conservation of key neuroendocrine actors
218 and of their sequences, the mutation of which may lead to severe pathologies, or by
219 highlighting common processes in the impact of environmental stressors and pollutants
220 leading to the disruption of the reproductive capacity of wild species, domesticated animals or
221 humans, in the frame of the “One health” concept.

222 223 **2.2 Bases of phylogeny**

In order to investigate and compare neuroendocrine systems in an evolutionary perspective, it is necessary to relate the data obtained in a given species to the phylogenetical position of this species. Phylogeny of vertebrates and metazoa is by itself an ongoing research topic, based on multiple disciplinary fields such as paleontology, comparative anatomy, embryology, and more recently molecular systematics and phylogenomics. We are using, in the present manuscript, recent and largely consensual advances in vertebrate and metazoa phylogeny.

2.2.1. Phylogeny of vertebrates (Figure 2)

All vertebrate species belong to a monophyletic clade, *i.e.* a group of species that consists of all the descendants of a common ancestor. Among the vertebrate clade, several “subclades” can be distinguished. The most ancient (or most basal) is represented by cyclostomes (such as lampreys and hagfish). Cyclostomes are the sister clade of all other vertebrates characterized by the innovation of the jaws and therefore called gnathostomes. The gnathostome clade is further divided into two sister clades, the chondrichthyans (such as sharks and ray fishes) and the osteichthyans. The osteichthyan clade is further divided into two major sister clades: (i) the actinopterygian clade that encompasses teleost fishes (the largest current group of vertebrates with more than 25,000 species including most fisheries, aquaculture and model fish species) and some other “fish” clades such as holosteans (gar); (ii) the sarcopterygian clade that encompasses the tetrapods including mammals, and also some “fish” species such as the coelacanth, representative species of actinistia, a basal group among sarcopterygians. The current vertebrate phylogeny highlights in particular that the name “fish” is not by itself phylogenetically relevant, as it may apply to species from very distinct vertebrate clades, such as cyclostomes (lampreys), chondrichthyans (sharks), actinopterygians (gar, zebrafish), and sarcopterygians (coelacanth). Thus, human and coelacanth are phylogenetically closer than coelacanth and zebrafish or than human and zebrafish.

249

250 2.2.2. Phylogeny of metazoa (Figure 3)

251 While the broad lines of vertebrate phylogeny remained similar to the traditional classification
252 based on paleontology, comparative anatomy and embryology, the recent advances in
253 molecular systematics and phylogenomics largely challenged the classification of other
254 metazoa (8, 170). We present here a most consensual phylogeny of the major clades of
255 metazoa. Bilateria, the major clade among metazoa, gather animals with a bilateral symmetry
256 (at least at the embryonic stage) and with three tissue layers (endoderm, mesoderm, ectoderm)
257 during embryogenesis so that they are also called triploblastics. Besides bilateria, the
258 respective classification of the basal groups of metazoa, such as cnidaria (corals), porifera
259 (sponges), and others, is still largely under debate. Bilateria encompass two major clades, on
260 the one hand, deuterostomes which include chordates and among chordate the vertebrates, and
261 on the other hand, protostomes which include two major sister clades, ecdysozoa (flatworms,
262 insects, crustaceans,...) and lophotrochozoa (annelids, mollusks, ...) (8, 608).

263

264 2.2.3. Phylogeny of molecular families *versus* phylogeny of species

265 Phylogenetical analyses of protein families of interest, such as hormones / neuropeptides /
266 receptors / enzymes, potentially involved in the neuroendocrine control of reproduction, are
267 performed in order to compare sequences between various vertebrate or metazoa species.
268 Phylogenetic trees of molecular families highlight protein sequence conservation or
269 divergence and lead to hypotheses on evolutionary relationships between sequences and
270 possible functional variations. The phylogenetic tree of a given protein family does not
271 always follow the phylogenetic tree of the corresponding species, which makes it possible to
272 infer further hypotheses on the duplication, divergence, convergence and loss of
273 corresponding protein-coding genes.

2.3. Origin and fate of duplicated genes

Gene duplications produce so-called paralogous genes, and are considered as major drivers of evolution, as they provide new gene pools allowing the emergence of novel functions, organs and regulatory processes.

2.3.1. Intra-gene duplication

Besides gene duplication, intra-gene duplication of exons also contributes to the evolution of neuroendocrine systems, as exemplified by the multiple copies of thyrotropin-releasing hormone (TRH) peptide coded by the TRH gene (397), or by up to three homologous gonadotropin-inhibiting hormone (GnIH) peptides coded by the GnIH gene (see section 5). Intra-gene peptide duplication may lead to the amplification of peptide production or, after mutations of some of the duplicated sequences, to the production of distinct peptides with potentially differential activities.

2.3.2. Local gene duplication

Gene duplication produces paralogous genes and may originate from local genomic events, targeting either a specific gene or a limited genomic region. If no major genomic restructuration occurs afterwards, local duplication events can be traced back in extant species genomes by tandem position or by a relatively close position of the paralogous genes on the same chromosome. For instance, a local gene duplication in early gnathostomes is hypothesized to be at the origin of the two gonadotropin receptors, LH receptor and FSH receptor, positioned in tandem in tetrapods, including human, as well as in basal sarcopterygian (coelacanth) and basal actinopterygian (gar) (468). The conservation of the tandem position throughout vertebrate evolution may be related to conserved coordination of

gene expression, *via* chromatin accessibility and common regulatory factors. In the primate lineage, a specific gene duplication of the LH beta subunit (LH β) gene, that occurred much more recently, is at the origin of the chorionic gonadotropin beta subunit (CG β), involved in the regulation of an innovative reproductive organ, the placenta; further CG β duplications led to up to six hCG β genes in human arranged in a gene cluster together with the LH β gene on chromosome 19 (for review: (522)) (see section 3).

2.3.3. Whole genome duplication

Gene duplications may also originate from whole genome duplication events (WGD), as proposed by Ohno in vertebrates (548). Gene paralogs stemming from WGD are thus named “ohnologs” by certain authors. It is now consensually admitted that two successive WGD, referred to as “1R” and “2R”, for “first round” and “second round” of whole genome duplications, have occurred at the base of the vertebrate lineage (Figure 2), even though the exact timing of the second WGD is still under discussion (for review: (284)). These 1R and 2R WGD, which occurred about 450 Million years ago, are still traceable in the current human genome, by fourway paralogous regions (paralogons) covering a large proportion of the human genome (145). It has been advanced that the two rounds of WGD may have contributed to the evolutionary success of the vertebrate lineage.

Genome sequencing of teleost fish models, such as medaka, fugu or zebrafish, revealed an additional WGD, referred to as 3R (for 3rd round of WGD) (for review: (484)) (Figure 2). When occurred this 3R WGD in the actinopterygian lineage event, remained under debate until recently, as more genomes became available including for species of key phylogenetic positions such as a non-teleost actinopterygian, an holostean, the spotted gar (72), or a basal teleost, an elopomorph, the eel (273, 274). These studies concluded that, in the course of actinopterygian evolution, the 3R would have specifically occurred in the teleost lineage, in

an early teleost ancestor before the emergence of the basal group of elopomorphs. This 3R event is thus also referred to as TWGD or TGD (teleost whole genome duplication) (586), and is hypothesized to have contributed to the diversification of this group, the largest among vertebrates.

2.3.4. Definition of homologous, orthologous, paralogous, or ohnologous genes

These definitions are important in order to analyze the molecular and functional relationships and diversification processes among molecular families including those involved in neuroendocrine systems. Homologous genes are present in the same or different species, and all derive from a common ancestral gene. Homologous genes include orthologous, paralogous and ohnologous genes. Orthologous genes are genes present in different species and evolved from a common ancestral gene in the course of speciation (emergence of new species over the course of evolution). Paralogous genes are present in the same or in different species and result from the duplication of a common ancestral gene, either *via* local gene specific duplication or *via* WGD. Ohnologs are paralogs resulting from WGD.

2.3.5. Fate of duplicated genes

Gene duplication produces two paralogs, which initially exert the same redundant function. In most cases, this redundancy leads to a rapid loss of one of the two paralogs, *via* accumulation of mutations due to redundancy-related lack of selective pressure. However, both paralogs may be conserved after duplication due to evolutionary selection related to amplification of initial function, or sharing of initial pleiotropic functions (subfunctionalisation), or emergence of a new function (neofunctionalisation). Duplications followed by gene amplification, subfunctionalisation, neofunctionalisation, or loss, are involved in the evolutionary scenarios of the neuroendocrine gonadotropic axis.

3. Origin and evolution of gonadotropins, the pituitary relay between brain and gonads in vertebrates

3.1. Vertebrate gonadotropins

3.1.1. Discovery of pituitary gonadotropins

A role of pituitary gland activity on the development of gonads was suggested as far back as 1910 (132) by studies showing that hypophysectomy leads to an atrophy of genital organs. The first experiment describing the stimulatory effects of bovine pituitary extracts on rat ovarian growth and luteinization was published in 1922 (180), demonstrating that the anterior part of the pituitary gland contains a gonadotrophic factor. It took a decade before this factor appeared to be composed of two distinct fractions in ewes, one responsible for growth of ovarian follicles and the other for luteinization (190). These two fractions were accordingly named follicle-stimulating hormone (FSH) and luteinizing hormone (LH), respectively. Technical improvement in glycoprotein purification methods, and notably the development of ion-exchange chromatography, made possible a better assignment of the roles of LH and FSH. In hypophysectomised rats, it was found that FSH acts on granulosa cells of the Graafian follicles and LH on the *theca interna* and ovarian interstitial tissue, the combination of the two stimulating estrogen secretion, ovulation and *corpus luteum* formation (834). The dimeric nature of LH, first suggested by Li and Starman (1964), was confirmed by Papkoff and Samy (1967) (576) who characterized two dissimilar subunits in ovine LH. The biological activity of the reconstituted dimer was finally demonstrated by De la Llosa and Jutisz (1969) (382).

Another factor was also purified from the bovine pituitary gland that stimulates the thyroid (126). Homology between this thyroid-stimulating hormone (TSH) and the gonadotropins was suggested after experiments demonstrating that mammalian LH and FSH are able to stimulate

the thyroid of teleost fish (203, 204). Soon after, it was established that LH, FSH and TSH have one interchangeable subunit, the glycoprotein hormone (GPH) α subunit, whereas the β subunit determines the hormonal specificity (609). The first amino acid sequence of an LH α subunit was deciphered in 1971 (428) and its identity with the FSH α subunit was demonstrated in 1974 (710). The first sequences of β subunits also appeared in the early 70s ((428) for LH; (417) for TSH; (710) for FSH), confirming the homology between thyrotropin and gonadotropin β subunits. It was thus established by the mid-seventies that the two pituitary gonadotropins and the thyrotropin belong to a family of dimeric glycoproteins that share the α subunit, whereas the three β subunits, which confer hormonal specificity, are derived from a common evolutionary ancestor.

The demonstration of the existence of two pituitary gonadotropins was laboriously extended to all tetrapod groups (for review: (309)); teleosts ((758), for review: (407); chondrostei (628); dipnoi (627); chondrichthyans (629)), showing that all jawed vertebrates are provided with the same pituitary gonadotropic molecules. Up to now, a single gonadotropin has been discovered in the cyclostomes, in hagfish (819) and in lamprey (741) even though, in this later species, the α subunit has still to be identified (739). Glycoprotein hormones (*stricto sensu*), like all other pituitary hormones, are not found before the emergence of vertebrates (83).

3.1.2. Non-pituitary gonadotropins

The presence of a luteotrophic factor in urine of pregnant women was first observed in 1927 (24), leading to the development of the first pregnancy detection test. This gonadotropic factor was shown to be produced by placental cells in culture (327) and more specifically by syncytiotrophoblast cells (485) and named human chorionic gonadotropin (hCG). The similarity with LH in terms of biological activity was rapidly observed (439) and its ability to bind the same receptor as LH was later demonstrated (92), hence the LH-CG receptor naming.

Eventually, the close structural relatedness of hCG to LH was confirmed when sequencing data were made available (765). The human CG β subunit has later been found to be expressed in the pituitary (61) and testis (53, 583). Pregnant mare serum was also shown to contain a gonadotropic factor (123) that was called pregnant mare serum gonadotropin (PMSG) before its origin as a chorionic cell product was recognized and its name changed to equine chorionic gonadotropin (eCG). It was later demonstrated that, unlike their human counterparts, eCG and eLH β subunits are encoded by the same gene (702). LH β subunit expression also occurs in the placenta of a marsupial (482) and possibly in diverse eutherian mammals (119).

3.1.3. Extra-pituitary expression of LH and FSH

LH and FSH are also expressed in the gonads and the brain. The first report of gonadal expression of gonadotropin described the immunological detection of LH in human and rat Leydig cells and that of FSH in Sertoli cells (849). LH β subunit transcripts were further characterized in elongated spermatids in the rat (910), and were found to possess an extended 5' UTR end resulting in the same coding sequence as the pituitary transcript apart from the first three amino acids of the signal peptide (909). In female rat, FSH β , LH β and the common α subunits are produced by theca cells, *corpora lutea* and oocytes, whereas granulosa cells only express LH subunits. The ovarian LH β subunit gene uses the same alternative promoter as in the testis (680). Expression of this transcript is reduced by administration of PMSG, which activates both LH and FSH receptors in non-equine species (249, 419). Interestingly, *in vitro* granulosa cell expression of LH β mRNA is also decreased in response to a GnRH agonist, likely through FSH receptor activation (425). Both LH and FSH are expressed in the Siberian hamster ovary with levels varying according to the estrus cycle but in an opposite fashion as in the pituitary (699). No specific role has been described for these gonadal gonadotropins. Whether gonadal expression of gonadotropins is a common feature in

mammals or other tetrapods remains to be clarified but this seems to be the case in teleosts (4, 172, 626, 705, 706, 728, 879, 882). It has to be noted that the seabream ovarian LH β subunit transcript is also extended in its 5' end, suggesting the existence of a conserved alternative and gonadal-specific promoter for the LH β gene. However, the expression of the two ovarian gonadotropins is up-regulated by GnRH in the sea bream (879). Ovarian LH β subunit expression in the sole also varies according to the ovarian maturation stage, like in the pituitary (706).

Another important site of expression of gonadotropins in teleosts is the brain (172, 496, 580, 705). It was notably observed in a cichlid that the two gonadotropins expressed in the preoptic area potentially play a regulatory role on pituitary expression of gonadotropins (574). LH is also expressed in rat hypothalamus in a manner that depends on the presence of a functioning pituitary (177). Brain gonadotropins may be involved in neuronal regulation of steroid synthesis (427).

3.1.4. Main regulators of gonadal function

Genetic mice models where either the FSH β (380) or LH β (442) subunit or the FSH (1) or LH (908) receptor is deleted show that ovarian differentiation and growth are not dependent on pituitary gonadotropin stimulation even if FSH stimulates proliferation of granulosa cells in pre-antral follicles. In teleosts, timing of pituitary gonadotropin expression as compared to gonadal differentiation also pleads for a process that does not involve gonadotropins (518). Mammalian FSH receptors are expressed in granulosa cells from the secondary follicle stage (follicles with at least two layers of granulosa cells) onward and LH receptor expression on theca cells rapidly follows. After puberty onset, FSH is indispensable for the cyclic recruitment of follicles (after oocytes have reached their maximal size) and terminal folliculogenesis. LH is involved in the final steps of pre-ovulatory follicle maturation,

allowing meiosis to resume and inducing ovulation (6, 239, 474). LH is responsible for the production of aromatizable androgens by theca cells. These androgens then reach granulosa cells where they are converted into estrogens under the stimulatory action of FSH (371, 708). At mid-cycle, granulosa cells of recruited follicles acquire LH receptor expression and initiate progesterone production, the stimulation of which is later relayed by hCG. Progesterone is essential for ovulation and for preventing further follicle maturation.

As for the ovary, pituitary gonadotropins are not required for testicular differentiation but FSH stimulates proliferation of Sertoli cells in prepubertal testis (399, 448). At puberty onset, FSH promotes Sertoli cell function but its importance for spermatogenesis depends on taxonomic groups (297). LH stimulates proliferation of adult-type Leydig cells responsible for the production of steroid hormones (792) and activates steroidogenesis and therefore, spermatogenesis.

3.1.5. A role for gonadotropin subunit monomers or homodimers?

The gonadotropin receptors are poorly activated by gonadotropin subunit monomers or homodimers. However, the hCG β subunit is produced in large excess in most epithelial cancers and is believed to play an autocrine angiogenic and anti-apoptotic role, possibly through interacting with components of cysteine-knot growth factor (and notably TGF β) receptor complexes (124, 303). Free glycoprotein hormone α subunit is also produced in excess by the pituitary and secreted throughout the menstrual cycle (255) and by the placenta (635). In the placenta, the free α subunit is much more potent than the intact hCG in acting synergistically with progesterone to induce decidualization of endometrial stromal cells (512) and stimulates prolactin release from human decidual cells (65). Interestingly, the free α subunit stimulates differentiation and proliferation of prolactin-producing cells in the foetal and postnatal mammalian pituitary gland (31, 42, 95) and prolactin release by frog pituitary

cells in culture (544). The action of the free α subunit is not mimicked by LH or hCG heterodimer, demonstrating that the free α subunit, like hCG β , may have a specific role independent on the activation of the gonadotropin receptors.

3.2. Structural characteristics of gonadotropins

The glycoprotein hormones are non-covalently linked heterodimers composed of an α subunit that is common to all gonadotropins and TSH and a specific β subunit that confers biological specificity. In all species, the pituitary gonadotropin subunits are transcribed from single genes although some teleost fishes may be provided with two α subunit genes, resulting from genome duplication in recent ancestors (407). The α subunit gene contains four exons, the first of which encoding the 5' untranslated region, the three others coding for a 92-100 amino acid-long protein excluding the signal peptide. All pituitary glycoprotein hormone β subunit genes contain three exons, the first one coding for the 5' untranslated region and, in some species, part of the LH β signal peptide. The second intron-splicing site is located at the same position in all β subunit genes.

3.2.1. Global folding and general characteristics

The most obvious characteristics shared by the α and all β subunits are the presence of one or two glycosylation sites at conserved position and a conserved arrangement of cysteine residues. The crystal structure of hCG was resolved almost simultaneously by two different laboratories (390, 883). The structure of FSH was later deciphered (206) demonstrating that the overall folding pattern of the two glycoprotein hormone dimers is very similar. Taking into account the high degree of conservation of the glycoprotein hormone subunits in vertebrates and in particular the special cysteine arrangements (with the exception of teleost FSH β subunit as related below), it is tempting to assume that this organization is conserved

among vertebrate gonadotropins. Both the α and β subunits belong to the large cysteine-knot family of proteins and more specifically to the TGF- β subfamily (13, 28, 271). They present a similar folding producing flat elongated structure organized in a head to tail orientation in the dimer. Each subunit contains four antiparallel β strands tightened with a central cystine-knot motif from which three hairpin loops are deployed so that loops 1 and 3 from one subunit are intertwined with loop 2 of the other subunit. The determining knot motif involves six cysteine residues from each subunit (Figure 4). Four of them bridge β 2 and β 4 strands with two disulphide bonds forming an eight-residue ring through which penetrates a third disulphide bond linking the two other cysteine residues from the β 1 and β 3 strands. The α subunits contain a total of 10 cysteine residues, the two additional pairs linking the β 1 to β 2 and β 3 to β 4 strands tying the amino- and carboxy-termini to the core molecule. The β subunits have twelve cysteine residues. In addition to those involved in the knot, two of them form a disulphide bridge linking together the tips of loop 1 and loop 3 and two others, seven amino acids apart from each other, are involved in an intra-chain bonding located at the end of the β 4 strand. The last two cysteine residues form a disulphide bridge between loop 1 and the C-terminal extremity that constitutes the buckle of the “fastening belt” that wraps the carboxy-end of the β subunit around the α subunit loop 2. This latter structure is of crucial importance for maintaining the stability of the dimer at the low concentrations encountered in the peripheral circulation (13, 888).

3.2.2. α subunits

The α subunit is globally well conserved across vertebrates, a feature that is expected since a mammalian α subunit is able to associate with a teleost LH β subunit to produce a heterodimer that retains most of the biological activity of the native teleost LH (78, 201). Such stability in structure probably results from the constraints imposed on the α subunit that has to efficiently

524 associate with three different β subunits. The α subunits show alternate variable and
525 conserved regions. The variable regions, where insertions/deletions are encountered, are
526 located at the level of loop 1 and loop 3 as well as in the amino-terminal end of the protein.
527 On the contrary, the most conserved regions lie in $\beta 2$, $\beta 3$ and $\beta 4$ strands and in loop 2. Great
528 apes α subunit sequences are characterized by a 4-amino acid-long deletion in the amino-
529 terminal end, at an intron-splicing site. Some teleostean or chondrosteian sequences also show
530 deletions at this site. Surprisingly, mutations of cysteine codons occur in some sequences.
531 This is particularly the case in hagfish (*Epatretus atami*) where cysteines C2 and C4 are
532 replaced by an arginine and a tyrosine, respectively. C2 is usually involved in the disulphide
533 bridge with C7 that is part of the cysteine knot motif whereas C4 bridges with C1 to move $\beta 1$
534 and $\beta 2$ strands closer to each other (Figure 4). There is only one clone identified and
535 sequenced in hagfish (819), so these apparent mutations might result from artefacts in the
536 cloning or sequencing process. Nevertheless, a different assignment of the cysteine residues
537 may be operating in this subunit with C1 replacing C2 in the bonding with C7 and the absence
538 of bonding between $\beta 1$ and $\beta 2$ strands. Substitutions in cysteine residues are also observed in
539 the α subunit of the Elephant shark (*Callorhynchus milii* - NCBI NM001292594.1) where C9
540 is replaced by an arginine, of the Tiger salamander (*Ambystoma tigrinum* - CN048018.1) with
541 C6 also replaced by an arginine, and the Arabian camel (*Camelus dromedarius* -
542 XM010987723.1) (but not *C. bactrianus* - XM_006178591.1 and *C. ferus* -
543 XM_010948966.1) with C2 replaced by an aspartic acid. Whether these substitutions
544 correspond to sequencing errors or to true mutations remains to be clarified. Two
545 glycosylation sites are overall conserved except in crows (*Corvus cornix* - XM010404527.2,
546 *C. brachyrhynchus* - XM_08640241.2 and *C. macrorhynchus* - AB563175.1) where the
547 asparagine at the junction of loop 2 with the $\beta 3$ strand is replaced by an aspartic.
548 Carbohydrate side chains are predicted to impact on synthesis and storage, on receptor

binding and signal transduction, and eventually on metabolic clearance of gonadotropins (271). Since three species at least out of this taxonomic group share this substitution, a compensatory mechanism should occur for these gonadotropins to assemble and elicit full biological activity.

3.2.3. LH β subunits

LH β subunits are 112-121 amino acid-long, with the exception of equine LH β where a 10 nucleotide-long deletion induces a shift in the reading frame leading to an extension of the carboxy-terminal end in very much the same as for hCG β (702). The lamprey gonadotropin β subunit (*Petromyzon marinus* - AY730276.1) is also extended at the carboxy-terminal side. If it is an ancestral characteristic, it has not been conserved in the hagfish (*Eptatretus atami* - AB546741.1), another cyclostome species. In comparison to the α subunit, there are no major insertions/deletions within the mature proteins apart for single or two amino acid-long deletion events in some species, occurring in the region of loop 2. The degree of conservation at the amino acid level is lower than in the α subunit. In addition to the twelve cysteine residues, conserved amino acids are found mostly within the β strands but also in the loops that seem to be more constrained than in the α subunit. LH and TSH β subunits usually have one glycosylation site conservatively located in the β 1 and the β 2 strand, respectively, whereas FSH β subunits have both of them. One glycosylation site is actually found in a conserved position in almost all LH β subunits. It is to be noted that, in the spotted green pufferfish (*Tetraodon nigroviridis* - CR706772.2) and in the fugu *Takifugu rubripes* - XM_003963794.2), two related species, the unique glycosylation site is displaced to the carboxy-terminal end, between C10 and C11, two cysteine residues that are linked by a disulphide bridge. The zebrafish (*Danio rerio* - BC162111.1) LH β subunit has a second site also at this position. Two glycosylation sites are also found in LH β subunits in primates

except in human. The two sites are located as in FSH β subunits. Remarkably, the gonadotropin β subunit of cyclostomes, the most basal extant vertebrate species, is provided with the same two glycosylation sites. It is not known whether cyclostomes have only one or two pituitary gonadotropins. All TSH β subunits have two additional amino acids inserted in loop 2 (467) so that the hormone identified in cyclostome that do not have these two additional amino acids most likely belongs to the gonadotropin lineage. It is not known if this GTH is homologous to LH or FSH or is ancestral to LH and FSH, hence the naming GTH for gonadotropic hormone (739, 741, 819). A third potential glycosylation site is found in the lamprey GTH β subunits in their specific carboxyl extension.

3.2.4. CG β subunit

The primate CG β subunit genes arose from a duplication of the LH β subunit gene just before the divergence between New World and Old World Monkeys (see 3.3 Origin and evolution of gonadotropins). These sequences are characterized by a frame shift in the coding sequence due to a single nucleotide deletion, 8 codons before the LH β stop codon. This event generated a carboxyl extension of the encoded protein including several serine residues that are O-glycosylated in trophoblast cells. One of the consequences of this higher glycosylation level is the higher half-life of hCG in the blood when compared to hLH (112).

Equine CG β subunits are encoded by the LH β subunit gene expressed in the trophoblast. Surprisingly, a similar carboxyl extension phenomenon occurred in equidae albeit due to a different mechanism. In equidae, a ten nucleotide-long deletion occurred, leading to the same frame shift as in primates (702).

3.2.5. FSH β subunit

The less conserved subunit is the β subunit of FSH. This is mainly due to their high

599 evolutionary rate in the teleost lineage (627). Up to twelve amino acid residues are deleted in
600 the most derived teleosts, the acanthomorphes, essentially in the loop regions. The most
601 spectacular feature of the teleost FSH β subunits is the rearrangement of the cysteine residues.
602 Although conserved in most basal teleosts including ostariophyses (carp and catfish related
603 species), cysteine C3, which is involved in the latch of the seatbelt loop with C12, is then lost.
604 The seatbelt loop is determinant for the ability of the dimer to keep associated once diluted in
605 the general circulation. Teleosts have developed alternative means to ensure the seatbelt to be
606 fastened. In more recently emerged taxonomic groups (clupeocephala), an additional cysteine
607 (which will be referred to as C0) is found at the amino-terminal end that is extended to the left
608 and includes amino acids aligned to the signal peptide in other taxonomic groups
609 (elopomorphes (341); salmonids (758, 761); percomorphes (225, 226, 373, 553, 866)). It was
610 found by mutating the hCG β subunit so as to reproduce this teleost-type cysteine pattern that
611 the seatbelt could be latched by a disulphide bridge between C0 and C12 (888). In
612 cyprinodontiformes, the mature sequence after cleavage of the signal peptide does not include
613 C0 (709). Instead, another cysteine residue is found either two amino acids downstream of the
614 usual C3 position or just following C5, and it is likely that these subunits use the natural
615 gonadotropin β subunit folding pattern. The cleavage site of the signal peptide has not been
616 characterized so far in ostariophyses. If the mature protein includes C0, their sequence would
617 totalise 13 cysteine residues. Another striking feature in FSH β subunits is the more flexible
618 position and number of glycosylation sites. FSH β subunits usually have two glycosylation
619 sites. The one on the β 1 strand is generally well conserved except in some teleosts. The other
620 site is absent or displaced to variable regions in most teleost species. In an extreme case, the
621 Atlantic halibut (AJ417768), the FSH β subunit is deprived of any glycosylation site. At the
622 opposite, a third site is occasionally found in some sharks, teleosts, turtles, birds and
623 crocodiles. The unique pattern of cysteine arrangements or glycosylation states of teleost

FSHs offers remarkable examples to investigate structure-function relationships. It is to be noted that most of these studies have been performed on mammalian hormones expressed in mammalian cells cultured at 37°C and thus, far from the low temperature at which most teleost gonadotropin assemble and act.

3.3. Origin and evolution of gonadotropins

3.3.1. Recent discovery of additional members of GPH family in mammals

In search for ligands for orphan G-protein-coupled receptors in the human genome, Hsu and his colleagues identified two new glycoproteins, also present in other vertebrate genomes, that share numerous characteristics with the glycoprotein hormone subunits (293). They were called GPA2 (GPHA2) and GPB5 (GPHB5) as for the second glycoprotein hormone related α subunit and the fifth glycoprotein hormone related β subunit. GPA2 and GPB5 are able to associate into heterodimer and the heterodimer is able to stimulate the TSH receptor but not the gonadotropin receptors (523). The heterodimer was therefore named thyrostimulin.

3.3.2. Ancient origin of GPA2/GPB5 before the emergence of vertebrates

These glycoproteins, which are found in most bilateria (293, 581, 640, 645, 663), are now referred to as GPA and GPB in invertebrates that lack the classical glycoprotein hormone subunits (83). In most investigated invertebrates, the genes encoding GPA and GPB are located close to each other without intervening genes (662), suggesting a functional or regulatory link between them. A leucine-rich repeat-containing receptor related to the glycoprotein hormone receptors (279, 437) was also identified in several invertebrate species (645). The fly receptor (LGR1) binds and is activated by the fly GPA/GPB heterodimer (749). Interestingly, in the parasitic wasp *Nasonia* (266), the leech *Helobdella* (832) and the myriapode *Strigamia* (833), three species that lack GPA and GPB, the homologous receptor is

also absent. Altogether, these data strongly suggest that the vertebrate glycoprotein hormone α and β subunits derive from a duplication of GPA and GPB, respectively, early after the emergence of vertebrates.

3.3.3. A limited role for vertebrate GPA2/GPB5 in reproduction

No consensus role for GPA and GPB in invertebrates have been proposed to date even if they may have been involved in specific functions in different species (640). In vertebrates, few data are yet available. Like $\text{GPH}\alpha$, GPA2 harbours two glycosylation sites, the position of the one just after loop 2 being conserved. The other one is located on the $\beta 1$ (by analogy with $\text{GPH}\alpha$) strand. GPA2 lacks the cysteine residues involved in the bonding between $\beta 1$ and $\beta 2$ strands. It contains, in addition to the six residues composing the cystine-knot motif, two cysteine residues that are believed to form a disulphide bridge between loops 1 and 3. These loops appear longer than in $\text{GPH}\alpha$. GPB5 is encoded by two exons with the same intron/exon splicing site as for $\text{GPH}\beta$ subunits. It harbours only one glycosylation site, located on the $\beta 3$ strand, just following the cysteine knot motif. The main difference between the GPB5 and $\text{GPH}\beta$ subunits is the absence of the carboxy extension that constitutes the seat belt. As mentioned earlier, this seat belt is essential for the stability of the dimer so it is believed that a GPA2/GPB5 dimeric structure may not be maintained once diluted into the general circulation (13). The thyrostimulin naming of the GPA2/GPB5 dimer is based on the ability of the recombinant dimer to stimulate the TSH receptor but not gonadotropin receptors (523, 552). It is further supported by the hyperthyroid phenotype observed in mice chronically injected with the recombinant dimer (552) and in mice ubiquitously overexpressing GPB5 (443). In the latter case, the thyrotropic effect was attributed to the dimer formed by the overexpressed GPB5 with the GPA2 naturally expressed in the thyroid to activate the TSH receptor. However, the thyrostimulin concept is not supported by the absence of obvious

thyroid phenotypes in GPB5 knocked-out mice (443, 552) except for a transient hypothyroxinemia in juveniles (907). Surprisingly, no GPA2-knocked-out mice have been described. The GPA2/GPB5 dimer is 10 to 20 times more active than TSH in stimulating TSH receptor (552). Taking into account the wide variety of tissues expressing GPA2 and/or GPB5 (293, 520, 523, 552) and the TSH receptor (874), it is conceivable that the GPA2/GPB5 dimer may act as a local activator of TSH receptor. However, numerous tissues do not seem to co-express GPA2 and GPB5 so that, as for the free α and hCG β subunits, other modes of action as monomer or homodimer must be explored for GPA2 and GPB5. In any case, no abnormalities in fertility were mentioned in GPB5 knocked-out mice (443, 552, 906, 907) so that a major role of the GPA2/GPB5 dimer or of GPB5 by itself in the control of reproduction is very unlikely.

3.3.4. Evolution of the GPH family in vertebrates

Taking advantage of the availability of sequenced genomes from species of phylogenetical significance, comparative synteny analysis between amphioxus (a pre-vertebrate chordate) and vertebrate glycoprotein hormone subunit loci allowed the reconstruction of their evolutionary history in vertebrates (467, 663). A first local duplication of a tandemly organized GPA and GPB locus occurred just before the radiation of vertebrates and the emergence of cyclostomes, giving rise to the vertebrate forms of GPA and GPB (GPA2 and GPB5) and to the ancestral glycoprotein hormone (ancGPH) α and β subunits (Figure 5). The *ancgpha* gene was maintained close to *gpa2-gpb5* whereas the *ancgph β* gene was translocated soon after the duplication. After the first round of WGD (1R), one copy each of *gpa2* and *gpha* was lost from one of the duplicated *gpa2-gpha-gpb5* loci, leaving two copies of *gpb5*, i.e. *gpb5a* in the remaining *gpa2-gpha* locus and *gpb5b*. After the second WGD (2R), only one copy of the duplicated *gpb5b* was retained. From the duplicated *gpa2-gpb5a-gpha* locus,

one copy of the duplicated *gpha* and one copy of the duplicated *gpa2-gpb5a* were lost, leaving a single *gpha* encoding gene and the remaining single copies of the tandemly organized *gpa2* and *gpb5a*. These two genes were kept in tandem in teleosts (663) and in the Coelacanth (Ensembl scaffold JH127632; unpublished data). *gpb5a* was lost in tetrapods that only retained *gpb5b*. The ancestral form of *gphβ* that was somehow parted from its original environment soon after the original, local duplication was duplicated at the 1R giving rise to an ancestral the gonadotropin β subunit gene (*ancgthβ*) and to an ancestral TSHβ subunit gene (*anctshβ*) (Figure 5). The 2R duplicated the *ancgthβ* to generate *lhβ* and *fshβ* genes. One of the duplicated copy of the *anctshβ* gene (encoding TSHβ2) was retained in chondrichthyes and in lungfish and coelacanth but was lost before the radiations of teleosts and tetrapods (467). Of note, after the Teleost-specific WGD (3R), of all duplicated *gph* genes only the duplicated *tshβ1* gene was maintained (encoding TSHβ3 or TSHβ1b according to a recent nomenclature), all other duplicated glycoprotein hormone subunit genes being lost (467, 663). As mentioned earlier, two copies of GPHα subunit-encoding genes may have been generated in some teleost species, resulting from recent, specific tetraploidization events. While a tandem duplication was at the origin of the glycoprotein hormone family in vertebrates, the most recently appeared glycoprotein hormone, CG, was also generated by a tandem duplication that occurred during the radiation of primates, just before the divergence between New and Old World monkeys, some 35 to 55 Million years ago (272, 460). Subsequent gene duplications led to a rising number of CGβ duplicates, that are not all functional (in human, 4 out of 6 CGβ genes are functional), up to about 50 copies in gorilla (169). The New World monkeys have only one CGβ and one LHβ subunit gene. Surprisingly, in the marmoset and probably in all New World monkeys, the LHβ gene has lost its pituitary functionality, and it is the CGβ gene that is expressed in the pituitary and in the placenta from specific promoters (514). The first duplication event probably affected only the LHβ gene but

subsequent duplications also concerned the neurotrophin NTF4 gene (also called NTF5 or NTF6) although only one copy retained its functionality. Surprisingly, phylogenetic analysis of LH β and CG β transcripts showed that CG β sequences tend to group with the LH β sequence from the same species instead of with CG β sequences from closely related species. This phenomenon was shown to be due to gene conversion *i.e.* nonreciprocal transfer of sequence information, where the LH β gene sequence and notably its first and second exons act as the parent for *cg β* genes conversion (460).

4. Origin and evolution of GnRH, brain conductor of reproduction in vertebrates

4. 1. Introduction

In the late 1920s, once the involvement of the pituitary in the processes of reproduction was demonstrated, systematic investigations were initiated to decipher the link between the hypothalamus and pituitary gonadotropin secretion (491, 614). Harris was the first to propose the hypothesis of neurohumoral regulation of gonadotropin secretion (192). The question that remained to be resolved was how information perceived in the CNS would be communicated to the pituitary gland. In the early 1960s, several investigators reported, in crude hypothalamic extracts, the existence of substances that specifically stimulated the secretion of luteinizing hormone (LH) or folliculo-stimulating hormone (FSH), and that were probably polypeptides (367). It was concluded therefore that the hypothalamus regulates the release of LH and FSH by means of two releasing hormones (LH-RH and FSH-RH), transported to the anterior pituitary *via* the hypothalamic portal circulation. From that moment, several teams devoted their efforts to the isolation and identification of LH- and FSH-releasing hormones. The isolation of the single substance able to stimulate the synthesis and secretion of both gonadotropins was independently achieved in 1971 from porcine and ovine brain by the groups of Schally (465) and Guillemin (16, 77), respectively. It was a decapeptide that was

initially termed LH-releasing hormone (LHRH) or LH-releasing factor (LRF), but the molecule is now generally referred to as gonadotropin-releasing hormone (GnRH). For this seminal discovery, Schally and Guillemin were awarded the Nobel Prize in Physiology or Medicine in 1977.

4.2. Origin and evolution of GnRH

4.2.1. GnRH in mammals

The first GnRH form isolated from pig and sheep is an amidated decapeptide with the sequence pQHWSYGLSPGamide (77, 465). This sequence is identical in almost all mammalian species investigated so far (556). As other neuropeptides, GnRH is synthesized as part of a larger precursor molecule called pre-proGnRH. The full-length cDNA encoding this precursor was initially cloned from a human placental library (687). In human, pre-proGnRH is a protein of 92 amino acids that consists of the decapeptide, extended at the N-terminus by a signal peptide, and at the carboxy-terminus by a Gly-Lys-Arg sequence necessary for enzymatic cleavage and carboxy-terminal amidation of GnRH. The 56 aa-residue sequence located in the C-terminal region of the precursor is called the GnRH-associated peptide (GAP). The architecture of pre-proGnRH is conserved in other mammals.

The mammalian GnRH gene is composed of four exons and three introns (688). Exon 1 contains a part of the 5'-UTR. Exon 2 encodes the rest of the 5'-UTR, the signal peptide, the GnRH decapeptide, the amidation/proteolytic processing motif and the N-terminal part of the GAP. Exon 3 encodes the central portion of the GAP. Exon 4 encodes the C-terminal part of the GAP along with the 3'-UTR.

Immunofluorescence and immunohistochemical studies using specific antibodies revealed that GnRH is primarily localized in neurons located in the hypothalamus, particularly in the arcuate-median eminence region and the preoptic area (36, 403). In the median eminence,

GnRH nerve terminals secrete directly into portal capillaries. The peptide is then delivered by the portal circulation to the adenohypophyseal gonadotrope cells (614). An important feature of the secretory activity of GnRH neurons is its pulsatile nature (43). The frequency and amplitude of secretory episodes are essential for the release as well as the synthesis of LH and FSH by gonadotrope cells (784).

It was shown that GnRH neurons arise from the nasal placode and migrate to their target regions in the hypothalamus during development (682, 881); for review:(880)) This finding is in agreement with the observations that humans deficient in GnRH also lack their sense of smell and with studies showing a loss of GnRH cells in animals with olfactory placode ablation (871, 880).

In 1994 was reported, for the first time in mammals, the occurrence of a second GnRH gene (347). Details regarding this second gene will be provided in the next section since it encodes a peptide whose sequence was already described in chicken since 1984 (500).

4.2.2. GnRH in other vertebrates: contribution to the discovery of multiple GnRHs

For a long time after it was discovered, GnRH was thought to have an invariant sequence because all mammalian peptides that were characterized were identical (643). This view was invalidated in 1982 when the first GnRH variant, containing the substitution Arg⁸→Gln, was isolated from chicken hypothalami (364, 365, 498, 499). Several other molecular isoforms were subsequently identified through peptide purification, cDNA cloning, and more recently data mining. They were primarily found in teleosts, but also in amphibians, elasmobranchs and cyclostomes, and even in mammals (for review: (556)). They were generally named according to the species in which they were initially isolated. However, a given form found in a particular species or group can exhibit a much wider distribution, making this nomenclature particularly confusing. For example, salmon GnRH (sGnRH) (703) is present in many other

teleost species, including medaka and zebrafish (381, 555). Likewise, the mammalian form of GnRH (mGnRH) is also found in frogs (127, 269) and fishes (228, 558) but not in the guinea pig (323).

In 1984, the occurrence of a second GnRH was demonstrated in the chicken, called chicken GnRH-II (cGnRH-II) in addition to cGnRH-I (500). Since then, it became evident that almost all vertebrate species are able to produce more than one GnRH form, each encoded by a peculiar gene (for review: (556)): two in most of them, including human (868) and even three, notably in teleosts (870) but also in lampreys (349, 704, 715, 737, 757). Very interestingly, cGnRH-II is present in all gnathostomes with exactly the same structure. As a result, in species that express two GnRH forms, the cGnRH-II variant is systematically present in combination with a second one which corresponds to mGnRH in most mammals (870), some amphibians (127) and fishes (228), or cGnRH-I in birds (498, 500) and reptiles (436). In teleost species possessing three forms, cGnRH-II is often associated with the sGnRH variant, plus a third form whose structure is more variable (619).

The peptides belonging to the GnRH family share several characteristics: (i) They all are decapeptides with residues 1, 4, 9 and 10 perfectly conserved as well as modified amino-(pGlu) and carboxy-terminus (NH₂) (248) (Table 1). (ii) They originate from preproGnRH precursors that exhibit the same features as those of mammals (248). (iii) The general organization of their genes is similar (188), suggesting they all share a common ancestral gene.

In the brain of species containing several GnRH forms, each variant exhibits a peculiar distribution. In gnathostomes, three major GnRH neuronal systems were recognized (163). The first one, called the ventral forebrain GnRH system, is composed of neurons mainly located in the preoptic area of the hypothalamus and projecting toward gonadotrope cells in the pituitary. The GnRH molecular form synthesized by these neurons is variable depending

on the species: *e.g.* mGnRH, cGnRH-I, frog GnRH (fGnRH), sea bream GnRH (sbGnRH) or guinea pig GnRH (gpGnRH). Functionally, this peptide corresponds to the hypophysiotropic GnRH form initially characterized by Schally and Guillemin. The second GnRH system, called midbrain GnRH system, is composed of neurons located in the midbrain tegmentum near the third ventricle. These neurons project throughout the brain, especially in the midbrain and hindbrain, but also in the pituitary in some teleost and amphibian species. They produce the cGnRH-II form. The third system, called the terminal nerve GnRH system, has so far been identified only in teleosts. Neurons of this system are mainly located in the terminal nerve ganglion near the olfactory bulb, and project primarily to the telencephalon but also widely into the whole brain, including the retina and the olfactory epithelium. They specifically express the sGnRH variant (556). It is to note that, in some teleost species, cells from the hypothalamic GnRH systems and cells from the terminal nerve GnRH system clearly overlap in the forebrain (232, 233, 502). It was also shown that neurons from both systems share a common embryonic origin: they arise in the olfactory system and migrate into the forebrain (2, 3, 233, 234, 557, 869).

4.2.3. Evolution of GnRH genes in vertebrates: impact of WGD

Because GnRHs are short peptides, their evolutionary relationship was difficult to establish solely on the basis of their primary structure (337). In 1998, a phylogenetic analysis of GnRH prepro-hormones from 23 species of bony fish and mammals revealed the existence of three evolutionarily distinct GnRH groups, named GnRH1, GnRH2 and GnRH3 (869). These three groups globally coincide with the three GnRH forms identified on the basis of their location in the brain: releasing form localized to the hypothalamus (GnRH1), form previously localized solely to midbrain nuclei (GnRH2), and form localized to the telencephalon in teleosts (GnRH3) (188).

Subsequent phylogenetic studies including newly discovered sequences confirmed this categorization, which is now widely accepted and is at the basis of the current nomenclature (248, 337, 556). The occurrence of three GnRH paralogous genes is also supported by synteny analysis (360, 381, 555, 643, 644, 790) since each GnRH gene is positioned in genomic regions containing common neighbors across teleost and tetrapod species.

GnRH1 and GnRH2 are clearly two “old” genes since the peptides they encode exhibit a very well conserved structure among gnathostomes. In contrast, GnRH3 has long been considered as a teleost-specific gene, suggesting a more recent emergence, possibly through the teleost-specific whole-genome duplication (3R) (248, 337, 556). However, this hypothesis was rejected when it appeared that genes surrounding GnRH3 in teleosts are also present in tetrapods (360, 381, 555, 790). The view that GnRH3 arose by an ancient duplication before the teleost-tetrapod split was recently confirmed by the finding of a GnRH3 ortholog in coelacanth and several species of elasmobranchs (219, 644, 903).

In lamprey, three members of the GnRH family of neuropeptides have been identified, named lamprey GnRH-I (lGnRH-I), lGnRH-II and lGnRH-III (349, 704, 715, 737, 757). The precise relationship between lamprey peptides and the three subtypes of GnRH in other vertebrates was difficult to resolve. Phylogenetic analysis initially led Sower et al. (2009) (740) to propose that lGnRH-II may represent a vertebrate GnRH2 ancestral form and to classify lGnRH-I and lGnRH-II in a fourth group of vertebrate GnRH peptides. Once again, both assumptions were refuted by synteny analysis showing that lGnRH-II is a GnRH2 ortholog while lGnRH-I and lGnRH-III are two copies of GnRH3 that probably arose through tandem duplication (143, 252, 644, 725). It should be noted that the presence of GnRH was suggested in the hagfish hypothalamus by both radioimmunoassay and immunohistochemistry, but the identity of the peptide remains to be determined (541).

It is now well accepted that the three GnRH paralogs appeared together through the 2R. In strong support of this view is the observation in the genome of many species that GnRH1, GnRH2 and GnRH3 loci, in addition to a fourth locus without GnRH but sharing homologous neighboring genes, are part of a same tetra-paralogon (360, 790, 903). Moreover, a GnRH-like gene recently characterized in amphioxus is positioned in a locus surrounded by syntenic homologs of the human GnRH tetra-paralogon (642). Taken together, these data suggest that four GnRH paralogs, including a putative GnRH4, were present in the last common vertebrate ancestor (360, 790) (Figure 6).

After 2R, the history of the GnRH family was driven, across vertebrate evolution, by multiple and independent gene loss events, leading to the diversity of GnRH currently known.

The GnRH1 gene occurs in all gnathostomes but not in cyclostomes, suggesting gene loss specifically in this latter lineage. The GnRH2 gene is currently the most represented GnRH gene in living vertebrates. No GnRH3 gene has so far been isolated from any tetrapod, while it is present in several groups of fish. It thus appears that this gene was likely deleted during the early evolution of the tetrapod lineage. Finally, the putative GnRH4 gene probably disappeared shortly after 2R without leaving any trace in current species (Figure 6).

Apart from these general considerations, additional species-, genus- or family-specific losses of a GnRH form subsequently occurred independently in different vertebrate lineages. For example, some teleosts lost GnRH1 (salmon, trout, goldfish, zebrafish, arowana) or GnRH3 (eel, catfish, butterfly fish). In elephant shark, only GnRH1 and GnRH2, but not GnRH3, were identified (536, 644). Also, certain mammalian species lost GnRH2 (rat, mice, cattle, sheep, chimpanzee), and thus now possess only GnRH1 (746). It is to note that no effect of the 3R can be recorded on the current number of GnRH genes in teleosts, suggesting massive gene losses after 3R. In contrast, two GnRH3 are present in sockeye salmon (25), probably

due to the salmon-specific whole-genome duplication (4R) (420), while two tandemly arranged GnRH1 exist in elephant shark (219) (Figure 6).

The detailed evolutionary relationship between the three GnRH paralogs is still not completely understood. Phylogenetic analysis shows that GnRH1 and GnRH3 sequences group into the same clade, suggesting they share a common ancestor (248, 349, 800). Moreover, in teleosts, GnRH1 and GnRH3 neuronal systems exhibit striking similarities regarding both their embryonic origin and their distribution in the brain (337, 556). Taken together, these data support the notion that 1R generated on the one hand the GnRH1-GnRH3 ancestor and on the other hand the GnRH2-GnRH4 ancestor. Although appealing, this scenario remains to be confirmed.

4.3. Origin and evolution of GnRH receptors

4.3.1. GnRH-R in mammals

GnRH receptors (GnRH-R) were initially characterized in the pituitary and several other tissues such as the brain, placenta and gonads, as specific binding sites with high affinity for mGnRH1 and its potent agonist or antagonist analogs (747). Some immortalized cell lines derived from neoplastic tissues also proved to be an important source of GnRH-R (747). One of them, the mouse pituitary α T3 gonadotrope cell line, led to the molecular isolation of the first GnRH receptor sequence, by expression screening for electrophysiological (809) or calcium responses (634) in *Xenopus* oocytes. This sequence provided the basis for the cloning of GnRH-R in several other species (506, 686).

GnRH-R is mainly expressed in gonadotrope cells of the pituitary, in agreement with its role in the synthesis and release of gonadotropins, but it is also present in extra-pituitary tissues including the brain (320), placenta, gonads, prostate, uterus and breast (108, 637). GnRH-R is also expressed in cancer tissues, either related (*i.e.* prostate, breast, endometrial, and ovarian

cancers) or unrelated (*i.e.* melanoma, glioblastoma, lung, and pancreatic cancers) to the reproductive system. Activation of GnRH-R was shown to inhibit proliferation of transformed cells making this receptor a therapeutic target for direct action of GnRH analogues on certain proliferating cells (422, 450).

Analysis of the primary sequence identifies the GnRH receptor as a member of the rhodopsin β -like G protein-coupled receptor (GPCR) family, which contains a characteristic seven transmembrane (TM)-domain structure (686). Unlike most GPCRs, which are intronless, the GnRH-R gene is composed of three exons and two introns (181).

A hallmark feature of the mammalian GnRH-R is the absence of a cytoplasmic carboxy-terminal domain, which is unique among GPCRs (686). As a result, this receptor is resistant to rapid desensitization and internalizes very slowly (142, 597). The extracellular loops (EC) and superficial regions of the transmembrane domains (TM) are responsible for receptor-ligand recognition and binding while the intracellular loops are involved in interacting with G proteins for signal transduction (196, 490).

In gonadotrope cells and gonadotrope-lineage cells, activation of the GnRH receptor stimulates a variety of intracellular signalling pathways (99, 525, 600). However, it is generally accepted that the primary effect of GnRH binding to its receptor is the activation of phospholipase C β (PLC β) through the G_{q/11} G protein and the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP₂) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃), which stimulates calcium release and activates protein kinase C (PKC) (247). These events lead to the synthesis and release of gonadotropins (747).

The presence of at least two GnRHs in most vertebrates, including mammals, suggested the existence of several cognate GnRH receptor subtypes (793). In support of this view, the occurrence of a second GnRH-R subtype (called GnRH-RII, as opposed to the first subtype now renamed GnRH-RI) was reported in non-human primates (488, 530). It is noteworthy

that the GnRH-RII subtype is either partially or completely silenced in a number of mammalian species (human, chimpanzee, sheep, cow, rat, and mouse) (487, 506, 507).

A study carried out in marmoset showed that the type II GnRH receptor is more widely distributed than type I receptor (488). As expected, GnRH-RI exhibits greater sensitivity to the hypophysiotropic GnRH form, GnRH1, than to GnRH2. Conversely, the GnRH-RII shows greater sensitivity to GnRH2 than to GnRH1 (304, 449, 488).

4.3.2. GnRH-R in other vertebrates: contribution to the discovery of multiple GnRH-R

The first non-mammalian GnRH-R was isolated from catfish in 1997 (778). Remarkably, this receptor exhibits a 49-amino acid cytoplasmic carboxy terminal domain that is lacking in the mammalian receptors. Moreover, it possesses a much higher affinity for GnRH2 than for GnRH1. A number of subsequent studies described the cloning of GnRH receptors in several other species, including trout (447), *Xenopus* (794), and chicken (754). In some species, such as in goldfish (305), bullfrog (855) and sea bass (503), the coexistence of two, three and even five distinct GnRH-R subtypes was reported, respectively. Three GnRH-R were also characterized in lamprey (330, 716). GnRH binding sites in GnRH-R type I and II forms are highly conserved but several amino acid residues in the second and fourth transmembrane domains confer selectivity toward GnRH1 and GnRH2 (122, 205).

Interestingly, at both the structural and functional levels, non-mammalian GnRH receptors resemble more closely the mammalian type II receptors than the mammalian type I receptors. Indeed, they all have a carboxy-terminal tail and a higher affinity (although sometimes modest) for GnRH2 than for GnRH1 (337). Moreover, in contrast to GnRH-RI, they show an Asp residue in transmembrane domain 2 that is conserved among members of the GPCR family. This Asp residue, that is replaced by an Asn residue in the mammalian GnRH-RI, is required for receptor activation (406, 488).

As the mammalian GnRH-RII, non-mammalian GnRH receptors are expressed in numerous tissues, in particular in reproductive organs. In species possessing several GnRH-R subtypes, each receptor exhibits a distinct expression pattern (248). Both mammalian GnRH-RII and non-mammalian GnRH receptors generally couple to the Gq protein and therefore mediate the intracellular production of inositol phosphates (99, 337).

4.3.3. Evolution of GnRH-R genes in vertebrates: impact of WGD

The evolutionary relationship between vertebrate GnRH receptor is still obscure, making it difficult to propose a consensual nomenclature (see (613) for a detailed review of the different nomenclatures proposed over time). As mentioned above, vertebrate GnRH receptors were generally subdivided into two major types (I and II) on the basis of both their structural (presence or not of a C-terminal tail) and functional (selectivity to individual GnRH peptides) features. Type I GnRH-R only contains the mammalian « tail-less » sequences, while type II GnRH-R includes all remaining sequences, from both mammalian and non-mammalian species. Such a categorization is well supported by numerous phylogenetic analyses in which GnRH-RI and GnRH-RII sequences actually group into two separate major clades (302, 613, 643, 644, 690, 776, 873).

Until recently, GnRH-RI sequences were only found in mammals, suggesting that this receptor evolved after lineage-specific gene duplication in early mammals (337, 643). This concept was eventually invalidated when sequences of GnRH-RI were found in coelacanth, elephant shark and little skate (644, 690, 873), indicating that the gnathostome ancestor already possessed a type I GnRH-R. Thus, functionally, the absence of the cytoplasmic tail in type GnRH-RI can no longer be viewed as an adaptation to mammalian physiology (873), as previously suggested by some authors (142, 794).

In contrast to the type I clade, the type II clade is characterized by a wide heterogeneity, since it includes sequences from species of very diverse origins. This heterogeneity is reinforced by the fact that most of these species possess multiple type II receptor forms, *e.g.* three in lamprey, some teleosts and amphibians, and up to four in coelacanth. Hence, recent studies subdivided type II clade into two major clades, called IIa and IIb (613, 644, 873). IIa and IIb can be further split into three and two groups, respectively. The first type IIa GnRH-R clade contains all three of the lamprey GnRH-R sequences plus one of the coelacanth paralogs. The second type contains the mammalian type II GnRH-R plus one of the coelacanth paralogs, while the third type contains GnRH-R sequences from teleosts, coelacanth, amphibians, reptiles and birds. The first type IIb clade also contains GnRH-R sequences from teleosts, coelacanth, amphibians, reptiles and birds, while the second type is exclusively composed of teleost sequences. It is noteworthy that the two IIb subtypes are not discriminated in the Williams's study.

At first sight, the logic of this breakdown is not obvious. Indeed, phylogenetic analyses, alone, are not perfectly suitable to explain the origin of the different GnRH receptor subtypes, and their evolutionary relationships. Recently, several studies have tried to revisit the history of the GnRH-R family in light of the 2R theory (360, 644, 690).

Following up a previous work (360), Sedifeh et al. (2014) (690) examined the conserved synteny of chromosomes harboring GnRHR genes. They identified three pairs of GnRH-R subtypes in three paralogous linkage groups, suggesting that an ancestral pair emerged through local duplication before 2R. According to their model, 2R thus led to the generation of 6 subtypes of GnRH-R in the vertebrate ancestor. However, this model is based on a phylogenetic analysis whose conclusions have been recently strongly challenged (644, 873). For instance, Roch et al. (2014) proposed that all three major GnRH receptor subtypes (types I, IIa and IIb) were already present in the vertebrate ancestor before 2R (644). These three

receptors would have been the products of two successive events of tandem duplication. According to their model, 2R theoretically led to the generation of 12 GnRH-R subtypes (Figure 7). However, due to multiple gene losses, only six of them were preserved. Thereafter, further losses could occur in the different vertebrate lineages, eventually leading to the current situation. This model is in good agreement with phylogenetic data, which identify a total of six GnRH-R subtypes. However, on the basis of practically the same data, Williams et al. (2014) propose a totally different scenario, in which only three GnRH-R genes were present in the gnathostome ancestor (873). By contrast, they argue that the current data do not resolve the number of GnRH receptors in the common ancestor of vertebrates and the actual impact of 2R.

Taken together, this information shows that further studies, combining both phylogenetic and syntenic data, will be needed to fully understand the evolution of the GnRH-R family in vertebrates.

4.4. Origin of the GnRH system before the emergence of vertebrates

In order to gain more insight into the origin of GnRH, intensive efforts have been made to hunt out GnRH-related peptides in phyla other than vertebrates.

4.4.1. GnRH and GnRH-R in non-vertebrate chordates

The first molecular evidence that GnRH occurs outside vertebrates was provided by the characterization of multiple GnRH-like peptides in tunicates, encoded by one or two different genes, depending on the species (5, 264, 618, 644). In several species examined, such as *Ciona sp.* or *Halocynthia sp.* (5, 264), pre-proGnRHs are multifunctional precursors, each containing the sequence of two to three tandemly arranged peptides. However, despite the unique organization of their precursor, almost all tunicate GnRH forms identified so far are

decapeptides including the six invariant amino acids, in positions 1–4, 9 and 10, found in vertebrates (644) (Table 1). It is noteworthy that the occurrence of both mGnRH and cGnRH-I reported by Di Fiore et al. (2000) (193) in *Ciona* could not be confirmed (5).

Search of the *Ciona* genome also led to the identification of four GnRH receptors (775). All these receptors possess a C-terminal tail similar to vertebrate type II GnRH-R, as well as several other structural features shared with vertebrate GnRH-Rs (643). At the functional level, only one tunicate receptor is able to activate the $G_{q/11}$ pathway and to trigger IP3 accumulation, while the three others provoke an increase of cyclic AMP formation through stimulation of G_s (775). At the evolutionary level, the four *Ciona* GnRH receptors cluster into a single clade at the root of the vertebrate GnRH-R one (644). Taken together, these data demonstrate unequivocally the existence in tunicates of a GnRH system homologous to that in vertebrates.

The occurrence of a functional GnRH system was also reported in amphioxus. However, the first Blast searches of the amphioxus genome allowed the identification of only GnRH-like receptor but not peptide sequences (776). Of the four amphioxus GnRH-R sequences found, only two, GnRH-R1 and GnRH-R2, cluster as expected, at the root of the chordate GnRH-R tree (642, 644). In contrast, the two others, GnRH-R3 and GnRH-R4, appear much more distant and do not group with chordate GnRH-R sequences (see below for more details). Nevertheless, the four amphioxus GnRH-R genes are positioned in the same locus surrounded by syntenic homologs of the vertebrate GnRH-R paralogon (642).

In 2009, a peptide with GnRH sequence identical to mammalian GnRH1 was purified from amphioxus (96) but this result proved to be artifactual (642). The occurrence of a genuine amphioxus GnRH-like gene was reported only five years later by using a more sensitive search methodology with hidden Markov models (642). The GnRH identity of this gene was confirmed by synteny analysis. However, the GnRH-like peptide encoded by this gene

exhibits a very atypical structure, pQILCARAFTYHTWamide, since of its 14 amino acids (aa) (and not 10), 3 only are conserved at positions 1, 5, and 7 with vertebrate GnRH2 residues (Table 1). It has been proposed that the amphioxus GnRH-like peptide may be cleaved to form a more active 7 aa-peptide (785). The amphioxus GnRH-like peptide acts as a ligand for amphioxus GnRH-R3 (642), but does not activate any of the three other amphioxus GnRH-R subtypes (642), indicating that the natural ligands of the latter receptors remain to be identified. It is to note that amphioxus GnRH-R1 and GnRHR-2 can be activated by vertebrate GnRH (642). Interestingly, a second GnRH-like peptide has been identified in the amphioxus genome (called GnRHv), but this peptide does not activate any of the four known amphioxus GnRH-R (642).

4.4.2. GnRH-like peptides and GnRH-R in other non-vertebrates

The first non-vertebrate GnRH-like molecule, at least clearly presented as such, was characterized in 2002 from a cephalopod mollusk, the common octopus (313). Octopus GnRH is a dodecapeptide that shares 7 residues with vertebrate GnRH2 from which it mainly differs by the insertion of two amino acids after position 1 (Table 1). The overall organization of the octopus GnRH precursor is the same as that of vertebrate pre-proGnRHs. Its cognate receptor was identified soon after and was demonstrated to have numerous similarities with chordate GnRH receptors (344).

Closely related peptides were subsequently identified in several other species of mollusks (58, 831, 912), annelids (832) and echinoderms (649, 695) (Table 1). All these newly identified peptides, together with the amphioxus GnRH-like peptide, were proposed to be classified as invertebrate GnRHs (invGnRHs), as opposed to vertebrate GnRHs (that also include the tunicate ones) (644). However, recent studies have shown that invGnRHs are probably not orthologous to GnRHs and should be renamed (see below) (613, 905).

1096

1097 4.4.3. Other GnRH-related peptides (AKH, CZR, ACP) and their receptors

1098 In 1998, the occurrence of a receptor structurally related to vertebrate GnRH receptors was
1099 reported in *Drosophila* (267). Several years later, the ligand for this *Drosophila* GnRH-type
1100 receptor was characterized and identified as a member of the adipokinetic hormone (AKH)
1101 family (745). Such a result was totally unexpected since AKH has been well known for a long
1102 time in insects (470, 748) but without apparent relationship with GnRH. However, taking a
1103 closer look, GnRHs and AKHs appear to share the N-terminal pyro-Glu residue and the C-
1104 terminal amide plus various identical residues depending on the species, in particular a
1105 conserved Trp at the third last position. It thus appears reasonable to consider peptides of the
1106 AKH family as possible GnRH homologs.

1107 AKH is an insect peptide first isolated from the locust *corpora cardiaca*, a functional
1108 equivalent of the pituitary gland in insects (835), for its ability to mobilize lipids from the fat
1109 body during flight (748). Many different forms (8-10 residues) of this peptide hormone were
1110 subsequently described in various insect species, with even two or three gene copies in some
1111 of them (216) (Table 1). AKH is also known as the red pigment-concentrating hormone
1112 (RCPH) isolated several years earlier in crustaceans (189) The first RCPH receptor has been
1113 recently characterized from *Daphnia* (456).

1114 In 1989, an AKH-like peptide was identified in the cockroach and named corazonin (CRZ,
1115 “corazon” being the Spanish word for ‘heart’) on the basis of its cardioacceleratory properties
1116 (830). Although slightly larger in size (11 residues), CRZ share several structural features
1117 with AKH (Table 1). Furthermore, their preprohormones have a similar organization
1118 indicating that the two neuropeptide precursor genes must have a common evolutionary origin
1119 (829). Like AKH, CRZ is expressed in neurosecretory neurons of the protocerebrum and
1120 transported to the storage lobes of the *corpora cardiaca* (622). The CRZ receptor was initially

characterized in *Drosophila* by a reverse pharmacology strategy (94, 582). Sequence analyses showed that CRZ, AKH and GnRH receptors are all evolutionarily related.

In 2006 Belmont et al. (2006) isolated from *Anopheles* a receptor with strong similarities to the AKH receptor but which is activated neither by AKH nor by CRZ (45). The natural ligand for this receptor was subsequently characterized as a new peptide called AKH/corazonin-related peptide (ACP) due to its intermediate structural features with AKH and CRZ (261).

In all species examined so far, AKH, CRZ and ACP originate from precursors that exhibit the same overall organization as those of vertebrate GnRHs, with the mature peptide immediately after the signal peptide. However, despite their structural similarities with other non-vertebrate GnRH-like receptors, the AKH receptors are specific for AKH and are not activated by ACP or CRZ. Similarly, the ACP receptors are specific for ACP and the CRZ receptors are specific for corazonin, showing that AKH, ACP and CRZ are three independent signaling systems (411).

For a long time, AKH, CRZ and ACP were thought to be confined to the arthropod clade, where they often (but not systematically) coexist in the same species (411). In 2009 the existence of an AKH-like peptide and its cognate receptor was reported in the nematode *C. elegans* (424), suggesting an older origin of the AKH signaling system. This notion was backed up soon later when it appeared that a functional AKH system is also present in mollusks (164, 265, 411), hemichordates (905) and echinoderms (785). Regarding the CRZ system, the same conclusion can be drawn from a recent study showing the presence of CRZ and its receptor in hemichordates and echinoderms (644, 785). In contrast, so far, ACP has been identified only in arthropods (905).

4.4.4. Evolutionary relationships between GnRH- and AKH-CRZ-ACP-like systems

The view that AKH, ACP, CRZ and GnRH peptides form a superfamily is generally well accepted (265, 318, 423, 492, 613, 644, 905). However, the precise relationships between CRZ, AKH, ACP and GnRH are poorly understood as illustrated by a very confused nomenclature (265, 613, 644, 801, 905). One of the major issues is whether AKH and CRZ neuropeptides can be both considered as orthologs to the vertebrate GnRH system. Unfortunately, this issue is not really addressed by phylogenetic analyses. In contrast, it appears likely that the invGnRH group previously defined by Roch (2014) (644) is not a monophyletic group (613, 801). It has thus been proposed to limit the name of GnRH exclusively to deuterostome GnRHs (613).

Regarding the receptors, the situation is also unclear. Phylogenetic analyses generally agree to recognize three major clades (265, 613, 644, 785). The first clade includes all chordate GnRH-Rs, except amphioxus GnRH-R3 and GnRH-R4, plus GnRH-R-like sequences from echinoderms, in other words most deuterostome GnRH-Rs. The second clade contains all arthropod CRZ-R sequences. It also encompasses amphioxus GnRH-R3 and GnRH-R4 plus some GnRH-R-like sequences from echinoderms and lophotrochozoans (annelids and mollusks). Surprisingly, among this second clade, are the octopus and *Aplysia* GnRH receptors, initially thought to belong to the GnRH-R group, as indicated by their name (344, 348). Finally, the third clade encompasses all arthropod ACP-R plus AKH-R sequences from arthropods, nematodes and lophotrochozoans. Depending on the authors, different clusterings of these clades were proposed and formed the basis of two main evolutionary scenarios (654) (Figure 8). The first scenario states that an ancestral CRZ-R, which was conserved in the ambulacrarians (echinoderms and hemichordates) and the lophotrochozoans (annelids and mollusks), duplicated twice independently and thus generated two lineages: the first leading to CRZ-R and AKH-R, subsequently AKH-R generated arthropod ACP-R in ecdysozoans, and the second leading to GnRH-R in chordates (Figure 8A). The second scenario states that

GnRH-R and CRZ-R might have been arisen via gene duplication in a common ancestor of bilaterians, and that a second gene duplication of GnRH-R might have generated AKH-R and ACP-R during the divergence between lophotrochozoans and ecdysozoans (arthropods and nematods) (Figure 8B). The main difference between the two models is that, in the first one, AKH-R/ACP-R and GnRH-R are not orthologous since they arose independently while, in the second one, they are orthologous. In contrast, both models agree that the CRZ-R gene was probably lost in urochordates, vertebrates and nematodes.

The second scenario was particularly detailed by Zandawala et al. (2018) who thus proposed to totally reconsider the classical nomenclature of the GnRH- and AKH-CRZ-ACP-like systems (905). According to these authors, who distinguish two major types of GnRH-like receptors, *i.e.* the (true) GnRH-R type and the CRZ-R type, the term AKH-R should be left out and replaced by GnRH-R in all bilaterian species, since AKH-R and GnRH-R are orthologous. Nevertheless, they suggest keeping AKH-R specifically in arthropods, together with that of ACP-R, its co-paralog. They also propose to change all the nomenclature of the invertebrate GnRH-like peptides on the basis of the receptor type that they activate. For example, the octopus GnRH, as well as its counterparts in other lophotrochozoans, should be renamed as CRZ because their cognate receptor clearly belongs to the CRZ-R type (344). Likewise, all AKHs from lophotrochozoans and non-arthropodian ecdysozoans (*e.g.* nematodes) should be renamed as (true) GnRHs.

As already mentioned, receptors of GnRH-R (GnRH-R1 and GnRH-R2) and CRZ-R (GnRH-R3 and GnRH-R4) types, have been characterized in amphioxus (776). In contrast, only one GnRH-like peptide was found in this group (642), that probably corresponds, for the reasons given above, to CZR. These data clearly suggest the existence of an authentic amphioxus GnRH that remains to be discovered.

All in all, the Zandawala's scenario appears very attractive, since it is based on the hypothesis of co-evolution between peptides and receptors, a process generally observed for neuropeptidergic signaling systems (492). However, further studies are needed to confirm this model, in particular to characterize the ligand-binding properties of the receptors in a larger number of species. For example, such studies would help to clarify the phylogenetic status of the different peptides recently identified in prawn (756), particularly the so-called GnRH, whose place in the Zandawala's nomenclature remains to be determined. The same remark applies regarding the so-called AKH2 and GnRH2 found in the marine annelid *Platynereis dumerilii* (129).

Phylogenetic analyses show that receptors of the GnRH/CRZ superfamily have close evolutionary relationships with receptors of the vasopressin (VP)/ocytocin (OT) family (492, 643). Interestingly, although they are not structurally related, GnRH2, OT and VP genes are tandemly arranged in several vertebral species (252, 360, 643, 790), also suggesting a possible common origin.

4.4.5. GnRH and GnRH-R before bilateria?

The nervous system in cnidarians is well known for its peptide wealth (245). As a matter of fact, a large number of neuropeptides have been isolated from different groups of cnidarians (211). Several reports show that coral tissues contain GnRH-like compounds (18, 812) but they have not been characterized yet. The occurrence of GnRH-like peptides has also been reported in the sea anemone genome (19). However, recent investigations failed to identify any GnRH-R-like sequence in cnidarian genomes (265, 613), suggesting that the GnRH-CRZ signaling system is a bilaterian innovation.

It is noteworthy that an earlier origin of the GnRH system was formerly proposed after the finding that yeast α -mating factor shows some structural and functional similarities to

vertebrate GnRHs (435). However, evolutionary relationships between both peptides are unlikely since α -mating factor is known to activate a receptor that does not belong to rhodopsin β -like GPCRs (329).

4.5. Functions of GnRH-like peptides: evolutionary perspectives

4.5.1. Reproductive functions of GnRH in chordates

In vertebrates, GnRH1 is the main GnRH form targeted to the pituitary. Its stimulatory effect on gonadotropin release is well established in many species. GnRH1 is thus considered as the major regulator of the hypothalamo–pituitary–gonadal axis whose stimulation leads to gametogenesis and steroid production in the gonads (556, 643, 921). Consistent with this notion, studies conducted in mice and humans show that GnRH1 null mutations result in hypogonadotropic hypogonadism and infertility (93, 97). In teleosts species lacking GnRH1, such as zebrafish, GnRH3 is believed to assume the hypophysiotropic role of GnRH1 (3, 744).

The action of GnRH1 is thus closely linked to the presence of a pituitary, which is a vertebrate innovation (643, 740). However, GnRH1 is also produced in and acting on other reproductive tissues. This is particularly the case in the gonads where, in numerous species of fish, amphibians, birds, reptiles and mammals, GnRH1 acts as a paracrine factor involved in the control of both gametogenesis and steroidogenesis (475, 477). This is also the case in the placenta (therefore specifically in mammals) where GnRH1 promotes trophoblastic cell invasion and regulates chorionic gonadotropin biosynthesis (670). In addition to its physiological actions, GnRH1 also regulates reproductive behaviors, including female lordosis (656) and male mating behavior (638) in rats.

As mentioned above, GnRH2 is primarily expressed in the vertebrate midbrain and is generally thought to have neuromodulatory actions (337, 556). Thus, intracerebroventricular

administration of GnRH2 promotes female reproductive behavior in various mammalian species (556). Likewise, GnRH2 stimulates female spawning behavior in goldfish (843). However, in some teleost and amphibian species, GnRH2 fibers originating from the midbrain were found to project, directly or indirectly, to the pituitary (125, 611, 921). As a matter of fact, GnRH2, as GnRH1, stimulates gonadotropin synthesis and secretion by pituitary gonadotrope cells (148, 489, 554).

GnRH3 is implicated in the control of reproductive behavior in teleosts. For instance, in cichlid fish, GnRH3-immunoneutralization decreases nest-building ability of males (542). Similarly, in medaka, terminal nerve GnRH3 neurons have an essential role for activating mating preferences based on familiarity (559).

In tunicates, GnRH induces the release of gametes, probably *via* a direct action on the gonads (779), suggesting that GnRH already exerted reproductive functions in the olfactores ancestor (the common ancestor of urochordates plus vertebrates), before the appearance of the pituitary.

4.5.2. Non-reproductive functions of GnRH in chordates

Both, GnRHs, and their receptors are expressed in numerous non-reproductive tissues in the central nervous system (cerebral cortex, hippocampus, cerebellum, ...) and in peripheral organs (bladder, adrenal, heart, ...) (722), suggesting that GnRH may have a variety of non-reproductive activities. In fact, GnRH1 is released in significant concentrations into the cerebrospinal fluid (CSF) to potentially act outside the hypothalamus (86, 721). GnRH1 can affect pituitary cells other than gonadotropes (722). In particular, GnRH1 stimulates GH release in goldfish (455) and chicken (677). A role of GnRH2 and GnRH3 on early brain regionalization and eye development has also been revealed by knockdown experiments in zebrafish (886). At the behavioral level, GnRH1 is involved in the control of anxiety and

depression was reported both in human and rodents (579), while GnRH2 influences feeding behavior (461, 777).

Interestingly, a role of GnRH in the control of metamorphosis has been recently observed in tunicates (342), suggesting that, even in the olfactores ancestor, GnRH is not just a reproductive hormone.

4.5.3. Roles of GnRH-like peptides in non-chordates

The first two GnRH-like peptides to be characterized in non-chordates were identified from octopus (313) and *C. elegans* (424). According to the new Zandawala's nomenclature (see above, 2018), these peptides correspond to CRZ-type and true GnRH-type forms, respectively. At the time of their discovery, both peptides were logically investigated for their reproductive functions. As a matter of fact, the octopus peptide was shown to stimulate oviduct contraction and gonadal steroidogenesis (312, 344), while the nematode peptide was described as a regulator of egg-laying behaviour (424). These findings were thus taken as a strong support to consider both peptides as GnRH homologs (in addition to the fact that they bind to GnRH-like receptors) (423). However, further studies showed that the reproductive functions of GnRH-like peptides are often marginal in non-chordate species.

As mentioned above, AKH- and CRZ-type signalling systems were first characterized in arthropods. Therefore, most of the functional data currently available are from this group, especially from *Drosophila* (905). In insects, AKH mainly regulates carbohydrate homeostasis, and lipid and carbohydrate mobilization, particularly during flight (216). AKH is also involved in other physiological processes related to locomotion and stress (265), but is generally not linked to reproduction (905). Only a few studies in the cricket (434) and the locust (509) indicate that AKH may have a role in reproduction. In crustaceans, RPCH, the AKH ortholog, modulates gut motility in the lobster (151) and ovarian maturation in the

crayfish, in addition to its role in background color adaption initially reported in the prawn (189). The functions of AKH-like peptides in other taxa are still poorly characterized. AKH has been recently identified in *Aplysia* (324) and functional assays indicate that it may modulate metabolism, feeding and gut motility, and also affect some gonadal parameters. Although this peptide is considered as a true GnRH according to the Zandawala's nomenclature (2018) (905). While the functions of ACP, the closest paralog of AKH in arthropods, are still unclear, in a recent study, ACP was shown to play a role in lipid metabolism and inhibition of oocyte proliferation in prawn (756).

As already indicated, CRZ was originally isolated from cockroach on the basis its cardiotropic properties (830). However, such an activity has been so far only documented in a few species. Since then, CRZ has been implicated in a wide range of functions in insects, including the initiation of ecdysis behaviors in the moth (362), induction of cuticular pigmentation in the locust (771), reduction of the spinning rate and pupal development in the silkworm (767), testicular development and spermatogenesis in the prawn (711). In ants, CRZ controls social behavior and caste identity (236). As for GnRH, the functions of CRZ in other taxa are still poorly known. The reproductive functions of CRZ in octopus have been mentioned above, but octopus CRZ (according to the Zandawala's nomenclature) has also non-reproductive functions, in particular on the heart and muscles (312, 344). In *Aplysia*, CRZ affects many processes including motor function, feeding and neuronal activities but has no significant effect on reproduction (753, 802).

Overall, GnRH-type and CRZ-type peptides are pleiotropic hormones that have both overlapping and specific properties, but do not exhibit clear patterns of functions emerges, thus making difficult to infer their ancestral functions in Urbilateria, the last common ancestor of bilaterians. The only (quasi) certainty is that the critical role of GnRH as a reproductive

activator is a characteristic unique to vertebrates (654), likely related to the innovation of the pituitary gland in this group.

5. Origin and evolution of brain RF-amide peptides in the limelight for reproduction

Two types of brain peptides, namely kisspeptin and GnIH/RFRP, have been subjected to most attention in the field of reproductive physiology since the early 2000s. Both belong to the superfamily of RF-amide peptides and have been proposed as new major actors in the neuroendocrine control of reproduction in vertebrates.

5.1. History and evolutionary relationships of the RF-amide peptides

5.1.1 Discovery of RF-amide peptides in mollusks

In 1972, a substance, designated peak C, was isolated in all major classes of the phylum Mollusca for its cardioexcitatory activity (9). Five years later, peak C was purified from cerebral ganglion extracts of the sunray venus clam, *Macrocallista nimbosa* (623). The neuropeptide identified, FMRFamide, was named after the letter abbreviations of its four amino acids, phenylalanine, methionine, arginine and phenylalanine, and its amidated C-terminal sequence (623). Since then, FMRFamide along with its structurally related neuropeptides named FMRFamide-related peptides (FaRPs) or FMRFamide-like peptides (FLPs) remains the best-investigated family of neuropeptides in mollusks.

5.1.2. RF-amide peptides superfamily in vertebrates

The first vertebrate member of the RF-amide family (peptides ending with Arg-Phe-NH₂) was isolated and sequenced (Leu-Pro-Leu-Arg-Phe-NH₂: LPLRFamide) from chicken brain in 1983 (152). This peptide was subsequently recognized as a fragment of a longer RF-amide peptide, gonadotropin-inhibitory hormone (GnIH) (for review: (806). Since 1983, a number

of neuropeptides sharing the typical C-terminal RF-amide (RFa) signature were discovered in all major animal phyla (174, 318, 904).

Dockray (2004) suggested designating the mammalian RF-amide genes, *farp-1* to *farp-5* in the chronological order they were described (153): the *farp-1* gene (601, 841) encodes two peptides, neuropeptide FF (NPFF) and neuropeptide AF (NPAF) (896); the *farp-2* gene (280) encodes prolactin-releasing peptide (PrRP) (280); the *farp-3* gene (281, 426) encodes two peptides, RFRP-1 and RFRP-3 also referred to as neuropeptide VF (NPVF) or GnIH (281); the *farp-4* gene (227) corresponds to the Kiss-1 gene encoding kisspeptin (or metastin) peptides (375, 549); the *farp-5* gene (104, 213, 322) encodes 26RFa, also named P518 or QRFP (104, 213, 322). These five distinct genes thus encode seven peptides in mammals (153, 630). The *farp* nomenclature based on chronology of discovery has not been followed by other authors (630). However, a similar classification into five groups has been adopted (for review: (826)) and further validated by phylogenetical analyses performed on sequences from various vertebrates including mammals, other tetrapods, teleosts and lamprey (570). These groups of RF-amide peptides were named by the authors: PQRFa (NPFF) group corresponding to *farp-1*; PrRP group corresponding to *farp-2*; LPXRFa (GnIH) group corresponding to *farp-3*; metastin (kisspeptin) group corresponding to *farp-4*; and QRFP (26RFa) group corresponding to *farp-5* (for review: (805)).

All the RF-amide peptides bind to G protein-coupled receptors (GPCRs). Dockray suggested, as for *farps*, to designate the receptors to the RF-amide peptides in the order they were identified as putative RFamide receptors: accordingly, *rfr-1* for PrRP (*farp-2*) receptor (280); *rfr-2* for RFRP-1 and RFRP-3/NPVF/GnIH (*farp-3*); *rfr-3* for NPFF and NPAF (*farp-1*) receptors (68, 176, 281); *rfr-4* for metastin/kisspeptin (*farp-4*) receptor (375, 513, 549); *rfr-5* for QRFP/26RF (*farp-5*) receptor (213, 322). Using phylogenetical analyses of more than 800 human GPCR sequences, Fredriksson (2003) showed five main families of GPCRs in human,

which they named glutamate, rhodopsin, adhesion, frizzled/taste2 and secretin (208). The rhodopsin family was divided into four groups: α , β , γ and δ (208). Kisspeptin receptor (also named GPR54 or *rfr-4*) belongs to the γ group, more specifically to the SOG receptor cluster, together with the receptors for non-RFamide peptides, somatostatin (S), opioid (O) and galanin (G) (208). Receptors of NPFF (*rfr-3*), GnIH/RFRP (*rfr-2*), PrRP (*rfr-1*) and QRFP (*rfr-5*) cluster within the β group, with receptors for non-RFamide peptides, neuropeptide Y (NPY), cholecystokinin, GnRH, tachykinin, ghrelin, and neuromedin U (208).

Several studies, based on synteny analysis and phylogenetic relationships of RF-amide peptides and receptors, provide new insights into the RF-amide peptide superfamily (for review: (904)). A gene encoding a PQRFa peptide has been identified in a cephalochordate, the amphioxus, indicating the presence of a *pqrfa* gene at least in a chordate ancestor (565). This ancestral gene likely gave rise to *gnih* (*farf-3*) and its sister gene *npff* (*farf-1*), via one of the two rounds of whole genome duplications (1R/ 2R) that occurred early in the vertebrate lineage ((565); for reviews: (807, 904)). The authors also reported phylogenetical relationships between NPFF, GnIH and QRFP (*farf-5*), suggesting a close evolutionary relationship between these three groups of RF-amide peptides (904). Kisspeptin (*farf-4*) has been proposed to be evolutionary more related to non RF-amide peptides, galanin and spexin, than to other RF-amide peptides, and proposed to be classified as a member of the galanin/spexin family ((359); for review: (904)). PrRP receptors likely share a common ancestry with NPY receptors as reported by Lagerström and collaborators (385), linking the PrRP group (*farf-2*) more to a non-RF-amide peptide family than to the other RF-amide peptide groups. The grouping of the various RF-amide peptide subfamilies/groups in a same RF-amide superfamily is thus currently a matter of debate (Figure 9).

5.2. GnIH (*farf-3*) and evolutionary-related peptides (NPFF and QRFP) (*farf-1* and *-5*)

1393 5.2.1. Discovery of GnIH in birds: direct inhibitory role on pituitary gonadotropins

1394 In 2000, Tsutsui and collaborators reported the isolation and characterization, from quail
1395 brain, of a novel neuropeptide, having an RFa motif at the C-terminus, which dose-
1396 dependently inhibits the gonadotropin, luteinizing-hormone (LH), release *in vitro* from quail
1397 anterior pituitaries. They named this peptide gonadotropin-inhibitory hormone (GnIH) (808).

1398 In the quail, starling and duck, the GnIH precursor mRNA encodes a polypeptide that can
1399 potentially be cleaved into three mature peptides with a C-terminal LPXRF-amide sequence
1400 (X=L or Q), named GnIH-related peptide-1 (GnIH-RP1), GnIH and GnIH-RP2 (quail: (671);
1401 starling: (814); duck: (207); for review: (378)). GnIH was identified as a mature endogenous
1402 peptide by mass spectrometry analyses, in the brain of quail (808), starling *Sturnus vulgaris*
1403 (814), zebra finch *Taeniopygia guttata* (788) and chicken (472), while GnIH-RP2 was also
1404 identified in the brain of quail (671).

1405 In 2005, Tsutsui and colleagues identified a GnIH receptor (898), using primers designed
1406 from the sequence of GPR147, a novel GPCR, also called NPFF receptor 1 (NPFFR-1) since
1407 its discovery together with another NPFF receptor (NPFFR-2 or GPR74) in mammals (68).
1408 As GnIH has higher affinity for NPFFR-1, the latter is considered to be the primary receptor
1409 for GnIH (68, 426).

1410 The direct inhibitory action of quail GnIH on LH release was confirmed in another bird, the
1411 chicken. An inhibitory effect of GnIH on LH release by pituitary slices was reported in the
1412 sexually immature female White Leghorn while it was not observed *in vitro* in sexually
1413 mature birds and nor on FSH release at both stages (446). In a hybrid of White Leghorn and
1414 Silkie Breed, GnIH inhibits LH release (but not mRNA expression), as well as FSH release
1415 and mRNA in pituitary explants (117).

1416 The direct effect of GnIH at the pituitary level is also supported by the detection of *gnih*
1417 mRNA in the pituitary of various bird species (quail: (898); starling and quail: (51)) and by

the colocalization of GnIH receptor immunoreactivity with LH β or FSH β mRNA expression in the chicken pituitary gland (446).

5.2.2. GnIH inhibitory role at the brain and gonadal levels in birds

GnIH may also directly influence GnRH secretion as GnIH-ir fibers are observed in contact with GnRH-ir neurons in many bird species (sparrow: (50); for review: (49); European starling: (814); zebrafish: (788)). Moreover, GnIH receptor mRNA is expressed in different parts of the brain in quail and starling as shown by PCR (51), and more specifically in both GnRH-I and GnRH-II neurons in European starling *Sturnus vulgaris* as shown by ISH/ICC (814).

Injection of GnIH rapidly reduces plasma LH and attenuates GnRH-induced rise in plasma LH in sparrow (49, 569). In quail, continuous administration of GnIH for 2 weeks decreases LH β mRNA levels (818). In the Pekin duck, icv injection of GnIH reduces plasma LH concentrations, while administration of GnIH-RP1 has no effect (207). One study reported no effect of GnIH on LH plasma levels in a bird species: in the Rufous-winged sparrow, GnIH does not affect basal or GnRH-stimulated plasma LH levels (149).

PCR analyses reveal the presence of GnIH as well as GnIH-R mRNAs in the testis, ovary and accessory reproductive organs (oviduct, epididymis and *vas deferens*) in starling and quail (51). Similarly, transcripts for GnIH and GnIH-R are detected in the testis of house sparrow *Passer domesticus* ((476); for review: (475)). In this latter species, GnIH decreases testosterone secretion from cultured testis (476). This indicates possible local, autocrine/paracrine actions of GnIH in the gonads in birds.

5.2.3. GnIH in mammals

The discovery of GnIH in birds has prompted investigations in mammals. The GnIH precursor cDNAs identified from mammalian brain encode two GnIH peptides, also known as RFamide-related peptides (RFRP): RFRP-1 and -3 (for reviews, see (804–806); rat: (281, 822); mouse : (281); Siberian hamster (813); bovine (212, 281, 900); monkey (815); human (281, 816)). Like avian GnIH and GnIH-RPs, all these peptides possess a common C-terminal LPXRFamide (X=L or Q) motif, with RFRP-1 being a C-terminal LPLRFamide peptide and RFRP-3 a LPQRFamide peptide (for review: (807)). In human and bovine (not in rat and mouse), a third peptide, RFRP-2, is also predicted, but is a LPLRSamide peptide or a LPLRLamide peptide, respectively (281). This RFRP-2 peptide could not be detected in an extract of human hypothalamus by using an avian GnIH antibody-conjugated immunoaffinity column and mass spectrometry, possibly due to its different C-terminal motif or because it is not processed from the precursor (816). The rat GPR147 does not respond to hRFRP-2, showing the importance of the C-terminal RFamide for the binding to the receptor (281, 816). The RFRP-2 sequence is absent from the RFRP precursor in the Siberian hamster (813). Li and collaborators suggested that the pig GnIH precursor encodes three RFRP peptides, two with an LPLRFamide C-terminal sequence and one with an LPQRFamide C-terminal motif (416). The authors reported also similar characteristics in the rabbit and golden hamster GnIH precursors (416).

In all mammalian species, as in birds, RFRP fiber terminals form close appositions with GnRH neurons (hamsters (377); rats (325, 377); mice (377, 885); sheep (726); monkeys (815); humans (816)). In the mouse, direct application of RFRP-3 on cultured brain slices decreases the firing rate of a subpopulation of GnRH neurons, and this effect is maintained when amino acid transmission is blocked, suggesting a direct suppressive action of RFRP-3 on the excitability of GnRH neurons (165).

In addition to its effects on GnRH neurons, GnIH may also act directly at the pituitary level

via its release in the portal blood in mammals as in birds. GPR147 (also referred to as NPFFR-1), is expressed in the pituitary in rat (281), Syrian hamster (230) and human (816), and RFRP-ir fibers are observed in the external layer of the ME in hamsters (230), sheep (118) and humans (815, 816). However, other studies using a different antiserum failed to detect RFRP-ir in the ME of rat brain and ip injection of the retrograde tracer Fluorogold did not label RFRP cell bodies (639). RFRP-3 inhibits GnRH-stimulated gonadotropin synthesis in pituitary gonadotropes in sheep *in vitro* (664), supporting a potential action at the pituitary level. In Artiodactylae, RFRP-3 inhibits GnRH-induced, but not basal, LH and FSH secretion and expression by primary cultures of pituitary cells (ewe: (118, 664); bovine: (332); pig: (415)). In rat, Pineda et al (2010) observed an inhibitory effect of RFRP-3 on both basal and GnRH-stimulated LH secretion (610), while other studies reported no effect (20) or an effect only on GnRH-stimulated LH release (517). In the Syrian hamster, Ancel et al. (2012) found no effect on either basal or stimulated LH release (17).

The presence of GnIH and its receptor in the mammalian gonads (Syrian hamster testis (914); human ovary (550); pig ovary and testis (416, 916)) suggests, like in birds, possible autocrine/paracrine regulations via a local gonadal GnIH system. Indeed, in the mouse, *in vivo* and *in vitro* studies show that GnIH/RFRP-3 treatment inhibits follicular development and ovarian steroidogenesis in the female (719), as well as testicular steroidogenesis and spermatogenesis in the male (22). Similarly, GnIH/RFRP-3 inhibits the synthesis and release of estradiol by ovarian granulosa cells (415) and of testosterone by Leydig cells (916) *in vitro* in pigs. Interestingly, a recent study investigating the role of RFRP-1 on ovarian activities reported a stimulatory effect of RFRP-1 on ovarian steroidogenesis at proestrus in the mouse, but an inhibitory action on ovarian folliculogenesis (141).

Using a mouse line with genetic inactivation of NPFFR-1, it has been demonstrated that the NPFFR-1 pathway is dispensable for preserved puberty and fertility ((401); for review:

(402)). To the best of our knowledge, there is no report on the possible impact of *gnih* (*npvf*) gene inactivation in mice.

5.2.4. Current studies on the presence and role of GnIH in the reproduction in other vertebrates

a. In other sauropsids

In sauropsids, apart from birds, three GnIH peptides (GnIH, GnIH-RP-1 and GnRH-RP-2) have been characterized in the red-eared slider turtle *Trachemys scripta elegans* (821), in the Chinese softshell turtle and in the anole lizard (for reviews: (566, 807)), and they all possess the common C-terminal LPXRFamide motif, like the avian and mammalian peptides. However, few studies have investigated their potential physiological roles. Brain localization of GnIH by ISH and/or immunohistochemistry has been reported in the Japanese grass lizard *Takidromus tachydromoides* (350) and the red-eared slider turtle (821). In the lizard *Calotes versicolor*, ovarian localization of GnIH has also been reported and GnIH is able to suppress ovarian GnRH receptor expression (718).

b- In amphibians: a GH-releasing factor (for review: (315))

In the bullfrog *Rana catesbeiana*, a RF-amide peptide, isolated from hypothalami, showed high (75%) sequence identity with quail GnIH (372). It was designated fGRP for “frog GH-releasing peptide” as it exhibits growth hormone-releasing activity (372). In parallel, the same peptide was isolated from the brain of the European green frog *Rana esculenta*, and named R-RFa for “Rana-RFamide” (104). The cloning of a cDNA for fGRP revealed that the deduced precursor encodes one fGRP and three putative fGRP-related peptides (fGRP-RP1, -RP2 and -RP3) (672). These four peptides were all identified as mature peptides and found to have a common C-terminal LPXRFamide with avian and mammalian GnIHs (824). Two of these peptides (fGRP and fGRP-RP2) stimulate GH and/or PRL release *in vivo* and *in vitro*, while

the other two (fGRP-RP1 and fGRP-RP3) have no effects ((372, 824); for review: (823)). None of them is able to modify the release of gonadotropins (372, 824). The localization in the amphibian brain is in agreement with other vertebrate distribution as positive neurons (cell bodies) are present in the periventricular region of the hypothalamus (372, 612, 673). In contrast, nerve fibers are widely distributed throughout the brain (612) notably in the olfactory system ((194, 612). An urodele, the Japanese red-bellied newt *Cynops pyrrhogaster* possesses four GnIH peptides (nLPXRFa-1, nLPXRFa-2, nLPXRFa-3 and nLPXRFa-4) but no functional studies have been performed yet (114). The GnIH system and its functional significance in amphibians has been recently reviewed (315).

c- In basal sarcopterygian and actinopterygian

In a basal sarcopterygian, the coelacanth *Latimeria chalumnae*, a GnIH precursor gene has been identified, encoding three putative LPXRFamide peptides and one LPXRFamide-like peptide, which align with human RFRP-1/quail GnIH-RP1, human RFRP-2/quail GnIH, human RFRP-3, and quail GnIH-RP2, respectively (for review: (516)).

In a basal, non-teleost actinopterygian, the spotted gar *Lepisosteus oculatus*, a GnIH precursor encodes three putative LPXRFamide peptides, which align with human RFRP-1/quail GnIH-RP1, human RFRP-2/quail GnIH, and human RFRP-3, respectively (for review: (516)).

d - In teleosts: positive and negative effects on gonadotropins

Up to now, in teleosts, only a single gene for GnIH has been identified as in the spotted gar. However, owing to the teleost specific WGD (3R), two GnIH genes would have been expected. This suggests the loss of one of the 3R-GnIH duplicated paralogs shortly after the 3R event.

Most of the teleost GnIH precursors encode three LPXRFamide or LPXRFamide-like peptides which align with human RFRP-1/quail GnIH-RP1, human RFRP-2/quail GnIH, and human RFRP-3, respectively (for reviews: (516, 807)). In some species, the precursor

encodes only two peptides which align with human RFRP-1/quail GnIH-RP1, and human RFRP-2/quail GnIH, respectively. Most GnIHs identified in teleosts possess the common C-terminal LPXRFamide motif observed in other vertebrate GnIHs.

Concerning the physiological role of GnIH in the control of the gonadotropic axis, the situation appears more complex in teleosts than in other vertebrates. In the goldfish, GnIH inhibits GnRH-stimulated *lh* β and *fsh* β expression by primary cultures of pituitary cells, with no effect on basal gonadotropin expression (625), while other studies describe either stimulatory, inhibitory or no effect on both basal and stimulated LH (release and expression), depending on the gonadal stage (510, 511). A stimulatory effect of goldfish LPXRa was observed on LH and FSH release by salmon pituitary cells (14). Similarly, goldfish LPXRa stimulates *lh* and *fsh* expression by whole pituitaries of grass puffer (700). In tilapia, treatment of pituitary cells in primary culture with tilapia LPXRFa-2 induces a significant increase in both FSH and LH release (60). In *Cichlasoma dimerus*, homologous LPQRFa-1 decreases LH and FSH release, while LPQRFa-2 is able to stimulate FSH release (whole pituitaries: (899)). In a basal teleost, the eel *Anguilla anguilla*, ongoing studies indicate that the three peptides encoded by the eel *gnih* gene exert an inhibitory effect on *lh* β mRNA expression by eel pituitary cells.

e- In cyclostomes (agnathans)

Tsutsui and colleagues in collaboration with Sower's laboratory (563) have cloned the lamprey GnIH precursor cDNA that encodes a precursor encompassing three GnIH peptides (lamprey LPXRFa-1a, LPXRFa-1b and lamprey LPXRFa-2). The lamprey GnIH peptides have a C-terminal PQRFa-2 motif, unlike most GnIHs, but like NPFF, in gnathostomes. *In vivo* administration of one of the lamprey GnIHs (lamprey LPXRFa-2) stimulates the expression of lamprey GnRH (GnRH3) in the hypothalamus and gonadotropin β mRNA in the pituitary (563). Thus, the authors suggest that GnIH may have emerged in agnathans as a

stimulatory neuropeptide that subsequently diverged to an inhibitory neuropeptide during the course of evolution from basal vertebrates to later-evolved vertebrates, such as birds and mammals (563).

5.2.5. Origin and evolution of GnIH and its receptors in vertebrates

Osugi and collaborators showed that agnathans possess both GnIH and NPFF genes, with the common C-terminal PQRamide motif (563, 570).

Tsutsui and colleagues hypothesized that vertebrate GnIH and NPFF genes may derive from a common ancestral gene present in protochordates (for review: (807)). In protochordates, a precursor cDNA of amphioxus PQRamide peptides was then identified. This precursor encodes three mature peptides characterized by immunoaffinity purification and mass spectrometry (565). The conserved syntenic region around the loci of the amphioxus PQRamide peptide gene, as well as of the GnIH gene and NPFF gene in vertebrates (565), suggests that GnIH and NPFF paralogous genes may originate from WGD in early vertebrates (for review: (567)) (Figure 9). As amphioxus PQRamide peptides inhibit forskolin-induced CRE-luciferase activity in COS-7 cells expressing the amphioxus PQRFa receptor 1 (565), the authors suggested that the common ancestral peptide of GnIH and NPFF has played an inhibitory role in reproduction in ancestral chordates (807). The inhibitory role of the ancestral peptide would have been conserved for GnIHs in mammals, birds and some teleosts, whereas a change from inhibitory to stimulatory role would have occurred in agnathans and some teleosts (807). In fact, the GH- and PRL-releasing activity of GnIH in amphibians with the lack of effect on gonadotropin secretion suggests a larger flexibility in the possible physiological roles of GnIH peptides in the course of vertebrate evolution.

Concerning GnIH receptors, two GPCRs have been identified in birds and mammals: (LPXRF-R or NPFFR-1 or GnIHR or OT7T022) considered as the primary GnIH receptor

and GPR74 (PQRF-R or NPFFR-2) with a lower affinity for GnIH (for review: (543)). In teleosts, up to three different GnIH receptor genes (*gnihrl*, *gnihr2* and *gnihr3*), that share high sequence identity with the mammalian and avian GPR147, have been isolated in zebrafish (913), goldfish (625) and common carp (599). This may reflect the impact of teleost specific WGD (3R) or of the additional WGD that occurred in some cyprinids (4R in goldfish and some carps). However, in most teleosts, only one receptor has been identified so far (grass puffer LPXRF-R (700); tilapia LPXRF-R (60); orange-spotted grouper GnIHR (858); clownfish GnIHR (113); tongue sole LPXRFa-R (853)). Further investigations are thus clearly needed.

Elphick and Mirabeau have identified a GnIH/NPFF-type receptor gene in the genome database of the hemichordate *Saccoglossus kowalevski* (174). Phylogenetic analyses grouped the receptors of vertebrates into NPFFR-1 (GPR147) and NPFFR-2 (GPR74), and the receptors of insects into SIFR (817). Deuterostomian NPFFR genes have already been proposed to share a common evolutionary origin with protostomian SIFR genes (492).

5.2.6. NPFF (PQRF) group (*farp-1*)

The first NPFF (PQRF) peptide to be reported was isolated from the bovine brain and characterized as a pain modulatory peptide (896). NPFF peptides possess a similar C-terminal structure (PQRFamide motif) as some GnIH peptides (for review: (577)). As previously discussed, *npff* and *gnih* genes are paralogous genes that likely emerged from WGD in early vertebrates. As GnIH precursors, the PQRFa precursor encompasses two to three putative mature peptides: NPFF and NPAF in mammals, NPFF and NPAF in teleosts, and PQRFa, PQRFa-RP1 and PQRFa-RP-2 in agnathans (lamprey and hagfish) (for review: (577)). NPFF peptides have been largely investigated for their role in the control of nociception (for review: (29)). Other actions have been also reported such as increasing arterial blood pressure

and water intake, while decreasing food intake in mammals (for review: (577)). Compared to GnIH or kisspeptin, few studies have been carried out to investigate the possible role of NPFF in reproduction. In teleosts, one study reported that bath application of medaka NPFF inhibits the pacemaker activity of terminal nerve GnRH neurons in the dwarf gourami (653). In agnathans, one of the hagfish NPFF peptides directly stimulates pituitary expression of gonadotropin β mRNA (568), while the lamprey peptides appear to possess a stimulatory effect only on GnRH2 secretion (140). These data suggest that PQRamide peptides may play a role in the reproductive system of lower vertebrates and that they might have adopted new functions during the course of vertebrate evolution (568).

5.2.7. QRFP (26RFa) group (*farp-5*)

In 2003, a new peptide family was simultaneously identified by three different laboratories (104, 213, 322). The first research group isolated the peptide from a frog brain extract, and named it 26RFa after its 26 amino acid sequence and RF terminal motif (104). The other two research groups identified the peptide while searching for ligands to an orphan GPCR (GPR103 also referred to as AQ27 or SP9155) (213, 322). Fukusumi and collaborators named it QRFP, after its pyroglutamylated arginine-phenylalanine-amide signature; the peptide consists of 43 amino acid residues (213). Jiang and collaborators (2003) named it P52 and its precursor protein, P518 (322). Comparative studies indicated that amphibian 26RFa and mammalian QRFP/P52 are orthologs (825). Phylogeny analyses of RF-amide peptides and receptors suggested a close relationship between QRFP (26RFa) (*farp-5*) on the one hand and the GnIH and NPFF groups (*farp-3* and *farp-1*) on the other hand, likely resulting from local gene duplication, preceding vertebrate WGD (904) (Figure 9).

A QRFP (26RFa) gene has been described in amphioxus (492, 889), suggesting that the gene existed in chordates before the emergence of vertebrates. As all vertebrates studied so far

possess a single gene, this suggests that duplicated paralogs resulting from the successive 1R, 2R WGD in early vertebrates and from 3R WGD in early teleosts, might have been lost (for review: (404)).

The main role reported for 26RFa/QRFP is the control of feeding behaviour with a potent orexigenic effect in mammals and birds, while it may also exert other various functions (for reviews: (102, 103, 105, 404, 825)). Concerning reproductive functions, *in vitro* and *in vivo* studies support the involvement of 26RFa in the control of the gonadotropic axis in mammals (528). 26RFa dose-dependently stimulates basal and GnRH-induced LH secretion by male and cyclic female rat pituitaries *in vitro* (528). Similarly, *in vivo* (icv or systemic) injection of 26RFa induces a significant increase of serum LH levels in cyclic and ovariectomized females (528). Patel and collaborators tested the more potent GPR103 ligand, QRFP43, *in vivo* and *in vitro* (594). They reported that icv injection of QRFP43 to male rats increases plasma LH and FSH levels; in contrast, intraperitoneal administration does not influence circulating gonadotropin levels (594). *In vitro*, QRFP43 stimulates GnRH release from hypothalamic explants from male rats and from the immortalized hypothalamic GnRH-producing neurons (GT1-7 cells) (594). In teleosts, one study in the goldfish reported that intraperitoneal injection of 26RFa increases plasma LH levels; the peptide may exert its action at the brain level, since 26RFa has no direct effect on LH release *in vitro* by primary cultures of pituitary cells (431).

5.3. A raising star in mammalian reproduction: Kisspeptin (*farp-4*)

5.3.1. Discovery of Kiss in mammals

In 1996, a metastasis suppressor gene for melanoma cells was identified and called Kiss-1... as a tribute to the chocolate speciality of the city of the authors (227). Then, in 1999, the cDNA of a novel GPCR was isolated from rat brain and named GPR54 (396). Since the

highest identity of this orphan GPCR was observed with the galanin receptors and since its cerebral distribution was similar to those of galanin receptors, the authors suggested that the endogenous ligand of GPR54 may have a peptidergic nature (396). Two years later, the natural ligands of GPR54 were isolated from human placenta (375). The Kiss-1 gene encodes a 54 amino-acid peptide which may be further processed into shorter peptides of 14 and 13 amino-acids (290, 549), all designated as kisspeptins (375). The peptide of 54 amino-acid residues was also named metastin (549). The 10-amino acid C-terminal fragment of kisspeptins (or kiss peptides) carries the biological activity (375). The functional importance of the C-terminal amidation was shown by the lack of binding and functional response for non-amidated synthetic kisspeptins (375).

A few years later, a pivotal role of kisspeptin in the control of reproduction was revealed. The discovery by three research groups (214, 648, 693) that inactivation of kisspeptin receptor (GPR54) leads to hypogonadotropic hypogonadism in human patients (loss-of-function mutations) and in mice (knock-out, KO) retained attention of reproductive endocrinologists and initiated intensive research on kisspeptin for many years. Hypogonadotropic hypogonadism was also observed in *Kiss1* KO mice (135). Conversely, mutations leading to higher resistance of kisspeptin to degradation (714) or prolonged activation of GPR54 (774) can induce precocious puberty onset in humans (for review: (714)).

5.3.2. Role of Kiss in the control of reproduction in mammals

a- Stimulation of GnRH neurons

Peripheral (subcutaneous, sc) or intracerebroventricular (icv) injection of kisspeptin increases plasma levels of gonadotropins and this response is abolished by the use of a GnRH antagonist (icv, mice: (237); icv, rats: (307); sc, rats: (464); icv, monkeys: (698)), suggesting a stimulatory effect of kisspeptin on gonadotropins via activation of hypothalamic GnRH

neurons. In addition, coexpression of GPR54 mRNA by GnRH neurons is observed in rat (307) and mouse (483). Icv administration of kisspeptin in sheep also induces a robust release of GnRH into the cerebrospinal fluid (483). Intraperitoneal (ip) injection of kisspeptin in wild-type mice stimulates LH and FSH release, but has no effect in *gpr54*^{-/-} mice (483). All these data define the kisspeptin system (ligand and receptor) as a major stimulator of the gonadotropic axis *via* induction of GnRH in mammals (rodents, sheep and primates). In rats and mice, two distinct subpopulations of kisspeptin neurons with different roles on GnRH/gonadotropic axis have been identified: the hypothalamic arcuate nucleus subpopulation is involved in the pulse mode of GnRH/LH release while the anteroventral periventricular nucleus subpopulation is implicated in the surge mode of GnRH/LH release (for review: (820)). A direct action of kisspeptin on GnRH neurons was demonstrated *in vitro*, as kisspeptin induces GnRH release from mediobasal hypothalamus (MBH) explants, while this did not occur in MBH explants from *Gpr54* null mice (770). Primary cultures of whole fetal rat brain respond to exogenous kisspeptin with increased *gnrh* mRNA expression (750). Using mouse GnRH-secreting neuronal cell lines (GT1-7 cells: (480); GN11 cells: (631)), two studies also showed a stimulatory effect of kisspeptin on GnRH secretion and mRNA levels (GT1-7 and GN11 cells: (540); GT1-7 cells: (780)); in contrast, another study using GT1-7 cells showed that kisspeptin fails to stimulate GnRH expression while increasing GnRH receptor transcriptional activity ((751); for review: (343)).

b- Direct action on pituitary and gonads

The expression of GPR54 in the pituitary gland and in particular on LH β cells in rat, ovine and human suggests a potential direct action on pituitary cells (for reviews: (218, 636)). In most mammals, kisspeptin-10 is able to stimulate LH secretion *in vitro* (rat: (527); bovine and porcine: (759); ovine: (727); baboon: (440)). However, other studies in rats have been unable to find any detectable action of kisspeptin on LH directly at the pituitary level (464, 783).

Few data are available on *in vitro* FSH regulation by kisspeptin in mammals. Either no effect on FSH release (baboon: (440)) or moderate stimulation of GnRH-enhanced FSH secretion (526) has been reported. Concerning the transcriptional regulation of gonadotropins, Witham and collaborators showed, using both the mouse pituitary gonadotrope cell line L β T2 and murine primary pituitary cells, that kisspeptin induces LH β and FSH β expression through the activation of KissR-1 signaling via PKC (876).

Expression of kisspeptin, as well as GPR54, in mammalian ovary (rat: (91); swine: (37)) and testis (mice: (854); goat: (660); primate: (306)) supports a role of the local kisspeptin system at the gonadal level. *In vitro* studies on the functional role of the kisspeptin system in gonads have so far given contradictory results in mammals, with no (mouse Leydig cells: (479, 854); Rhesus monkey testes: (769)) or stimulatory effect on steroidogenesis (swine granulosa cells: (38); goat Leydig cells: (661)). In addition, kisspeptin was shown to stimulate fertilization capacity of mouse spermatozoa (292).

5.3.3. Multiple Kiss and Kiss receptor genes in vertebrates: impact of WGD

a- 1R and 2R WGD origin of multiple Kiss genes followed by gene losses during vertebrate evolution (Figure 10)

While, in rodents, a single gene (*Kiss1*) is present, up to three *Kiss* genes have been identified in other vertebrate lineages including cyclostomes (2 genes), chondrichthyes (2 or 3 genes), actinopterygians (1 or 2 genes), basal sarcopterygian (coelacanth: 3 genes), amphibians (up to 3 genes), sauropsids (0, 1 or 2 genes), as well as in non-rodents mammals (1 or 2 genes). Phylogenetic analysis classified the identified *Kiss* genes into three different clades (i.e., *Kiss1*, *Kiss2* and *Kiss3* clades, leading to a phylogenetically-based nomenclature according to Pasquier and collaborators (587, 592). The current three *Kiss* genes may derive from a single ancestral gene duplicated through the two successive WGD (1R and 2R) in early vertebrates

(for review: (587)). These 1R and 2R events should have yielded four different *Kiss* genes in vertebrates, and syntenic analysis supports the potential existence of a fourth *Kiss* gene (*Kiss4*) in early vertebrates (587, 592).

The current diversity of *Kiss* gene numbers (from 0 to 3) in extant vertebrate species is the result of multiple and independent pseudogenization processes and gene loss events during vertebrate evolution that occurred after the 1R and 2R events (for review: (587)). The loss of the putative *Kiss4* gene would have occurred early in vertebrate evolution (shortly after the 2R) as it is absent in all extant species of key phylogenetical positions. Additional *Kiss* gene loss events would have happened, as only a few extant representative species of chondrichthyans (elephant shark) and sarcopterygians (coelacanth and *Xenopus*) possess three *Kiss* genes. *Kiss3* would have been lost independently in early actinopterygians and early amniotes, while *Kiss1* would have been lost independently in some teleosts and sauropsids, and *Kiss2* in some sauropsids and some mammals. The *Kiss1* and *Kiss2* genes are thus the most frequent *Kiss* genes in extant vertebrates. Among sauropsids, both *Kiss1* and *Kiss2* genes are present in some groups such as chelonians (turtle) and crocodilians, while *Kiss1* has apparently been lost independently in some squamates (anoles) and in birds. Furthermore, *Kiss2* has undergone pseudogenisation and loss during bird evolution, leading to the lack of *Kiss* in some species such as the chicken, falcon or parrot (591). In mammals, *Kiss1* and *Kiss2* are both present in a prototherian mammal (platypus), while *Kiss2* has undergone pseudogenisation and loss in metatherian (opossum) and eutherian mammals (for review: (587)). Although a *Kiss2*-like gene is present in the genomes of primates including humans, due to the lack of amidation signal in the precursor, the endogenous *Kiss2* peptide may not be functional or produced (564).

While teleost 3R WGD (TWGD) should have generated additional *Kiss* paralogs, extant teleost species do not possess more *Kiss* genes than a non-teleost actinopterygian (spotted gar)

(*Kiss1* and *Kiss2*) (592). The lack of impact of TWGD suggests a massive loss of 3R-Kiss paralogs shortly after the 3R event. Furthermore, additional loss of *Kiss1* led to the presence of a single Kiss gene (*Kiss2*) in some teleosts such as the tetraodon and stickleback (587).

b- 1R and 2R WGD origin of multiple Kiss receptor genes followed by gene losses during vertebrate evolution (Figure 11)

While, in mammals, only a single gene encodes kisspeptin receptor (*KissR*), several *KissR* genes have been identified in other vertebrates including chondrichthyes (2 genes), teleosts (1, 2 or 3 genes), amphibians (3 genes) and sauropsids (0, 1 or 2 genes) (for review: (587)). As for *Kiss* genes, the multiple *KissR* genes may have arisen from 1R and 2R, so that the potential existence of four *KissR* paralogs in vertebrates has been hypothesized (361, 398). Actually, a fourth *KissR* has been discovered in extant representative species of basal sarcopterygians (coelacanth) and actinopterygians (spotted gar). Phylogenetic analysis classified the identified *Kiss* genes into four different clades (*i.e.*, *KissR1*, *KissR2*, *KissR3* and *KissR4* clades), according to the nomenclature by Pasquier and colleagues (587, 589). Phylogenetic and syntenic analyses indicate that these four paralogs likely resulted from 1R and 2R WGD ((589, 592). This suggests that a *KissR* ancestral gene was present before the emergence of vertebrates. In agreement with this hypothesis, *KissR* homologous genes have been identified in non-vertebrate deuterostomes (174). The *KissR1* and *KissR3* clades are more closely related to each other than to *KissR2*, and likely represent sister clades stemming from 2R (587). A phylogenetic reconstruction of a gene family associated with the *KissR* paralogon, the PALM family (298), also supports the hypothesis that 2R gave rise to *KissR1* and *KissR3* sister paralogons on the one hand, and of *KissR2* and *KissR4* sister paralogons on the other hand.

As for the *Kiss* genes, after the 1R and 2R events, the history of the *KissR* family was driven, throughout vertebrate evolution, by multiple gene loss events leading to the current diversity

of KissR. *KissR4* has been lost independently in the actinopterygian and sarcopterygian lineages. In actinopterygians, this event has likely occurred in a teleost ancestor after the emergence of holosteans (e.g. the spotted gar still possesses the four KissRs). Among sarcopterygians, *KissR4*, which is still present in a basal species (coelacanth) in some sauropsids (chelonian and squamates) and in prototherian mammals (platypus), has been lost independently in the amphibian lineage, in some sauropsids (crocodilians) and in the common ancestor of metatherian and eutherian mammals, including human which possesses a single KissR (*KissR1*).

As for Kiss, due to massive gene losses, no effect of the teleost-specific TGWD can be recorded on the current number of *KissR* in teleosts (587, 589, 592). This is further supported by a recent study in pejerrey *Odonthesthes bonariensis* including phylogenetic analyses (791).

c- Gene conservation or losses and variations in Kiss/KissR couples

Comparison of the evolutionary histories of *Kiss* and *KissR* families (Figures 10 and 11) highlights both common features and divergences (587). Four *Kiss* and four *KissR* genes arose from 1R and 2R early in the vertebrate lineage, followed by repeated independent gene loss events throughout vertebrate radiation. As a consequence of the independent and asynchronous losses of *Kiss* genes, as well as of *KissR* genes, the extant vertebrate species present various combinations of putative Kiss and KissR couples. For example, the same two *Kiss* genes (*Kiss1* and *Kiss2*) have been conserved in a prototherian mammal (platypus) and in some teleosts (e.g. zebrafish, seabass) but together with the conservation of different receptors (*KissR1* and *KissR4* in platypus, versus *KissR2* and *KissR3* in zebrafish). Likewise, unmatching numbers of *Kiss* and *KissR* genes are present in some species, such as three *Kiss* genes versus four *KissR* genes in a basal actinopterygian, the spotted gar and a basal sarcopterygian (coelacanth), or two *Kiss* genes versus three *KissR* genes in a basal teleost, the eel (587, 592). Such variations in the putative couples between Kiss and KissR paralogs

1817 reveal a lack of maintenance and co-evolution of specific Kiss/KissR couples during
1818 vertebrate evolution. This may have been favored by the promiscuity of Kiss receptors
1819 towards various Kiss peptides, related to the high conservation of the 10 amino-acid C-
1820 terminal biologically active sequence (kisspeptin-10 or Kp-10) (398, 413, 561). In species
1821 where multiple *Kiss* and *KissR* paralogous genes have been conserved, differential
1822 physiological roles related to subfunctionalisation or neofunctionalisation may have emerged
1823 between paralogs.

1825 5.3.4. Current studies on the role of Kiss in reproduction in non-mammalian vertebrates

1826 a- In amphibians and reptiles

1827 In amphibians and reptiles, few functional studies are available and concern the action of
1828 kisspeptin on the gonads. In the anuran amphibian *Rana esculenta*, *in vitro* Kp-10 treatment
1829 induces testicular expression of both *gpr54* and estrogen nuclear receptor α , *ER α* (109). In
1830 this species, *ex vivo* treatment of testis with Kp-10 stimulates spermatogenesis (110, 111) and
1831 upregulates the expression of testicular *ER β* , *gnrh 1* and 2, as well as the three types of *gnrh*
1832 receptors (110). All the effects of Kp-10 in amphibians are counteracted by Kp-234, a
1833 kisspeptin antagonist (109, 110). In the reptile *Uta stansburiana* (side-blotched lizard), intra-
1834 coelomical treatment with kisspeptin up-regulates plasma testosterone levels (531).

1835 b- In teleosts: positive and negative effects on reproduction

1836 Even before the demonstration of colocalization of GPR54 on GnRH neurons in mammals
1837 (483), Parhar and collaborators reported that kisspeptin receptor (KissR2) localizes to
1838 hypothalamic GnRH neurons in tilapia, using laser-captured single GnRH neurons (578).
1839 Similarly, in the cichlid fish *Astatotilapia burtoni* (246) and striped bass *Morone saxatilis*
1840 (919), GnRH1 neurons express KissR2 mRNA. In the chub mackerel *Scomber japonicus*,
1841 GnRH1 neurons in the preoptic area co-express KissR1, but not KissR2 (545). Kiss1 and

1842 Kiss2 neurons show differential connections with GnRH neurons in the zebrafish brain (697,
 1843 732).

1844 In agreement with the expression of KissR by GnRH neurons, effects of kisspeptins on GnRH
 1845 neurons have been demonstrated in various teleost species. Kiss1 and Kiss2 peptides have
 1846 opposite effects on the electrical activity of hypophysiotropic GnRH3 neurons in adult
 1847 zebrafish: Kiss1 stimulates, while Kiss2 inhibits neuronal activity (915). In the striped bass
 1848 *Morone saxatilis*, only Kiss2 (but not Kiss1) upregulates the expression of the
 1849 hypophysiotropic *gnrh1* by *in vitro* brain slices (920). In contrast, in hypothalamic explants of
 1850 the half-smooth tongue sole, Wang and colleagues showed that Kiss2 has no effect on either
 1851 *gnrh2* or *gnrh3* mRNA levels (852). *In vivo* studies reported either no (zebrafish *gnrh 2* and *3*:
 1852 (366); grouper *gnrh3*: (707); hybrid bass *gnrh 2* and *3*: (919); yellowtail kingfish *gnrh1*:
 1853 (535); male chub mackerel *gnrh1*: (546, 691, 692)), stimulatory (grouper *gnrh1*: (707)) or
 1854 inhibitory (striped bass *gnrh1*, *2* and *3*: (918)) effects of Kiss peptides on brain transcript
 1855 levels of *gnrh*. Depending on the administration routes, in the female chub mackerel, both
 1856 stimulatory (sc (692)) and inhibitory (icv (546)) effects of Kiss2 have been reported on brain
 1857 *gnrh1* mRNA levels. These *in vitro* and *in vivo* studies thus indicate variable effects of
 1858 kisspeptins on GnRH in teleosts.

1859 Concerning the effect of kisspeptin on the pituitary in teleosts, direct (*in vitro*) stimulatory
 1860 action of kisspeptin 2 (Kp2) on pituitary LH secretion was reported in goldfish (895), striped
 1861 bass (918, 920) and sea bass (179), but no effect of Kp1 was observed in goldfish (413) and
 1862 sea bass (179)). In contrast, in the European eel, heterologous and homologous Kiss peptides
 1863 all directly inhibit the expression of *lh*, with no effect reported on *fsH* (588, 590). In the
 1864 striped bass also, Kp1 is generally ineffective but, at high doses, can inhibit *lh* expression
 1865 (918, 920). A few studies also report a stimulatory effect of kisspeptins on FSH (striped bass,
 1866 Kp1 and Kp2 (918, 920); sea bass, Kp2 (179)).

In vivo stimulatory (goldfish (413); sea bass (185); seahorse *Hippocampus erectus* (911)) or no (goldfish (524)) action of kisspeptins on gonadotropins have been described in teleosts. In the striped bass, kisspeptin action depends on the stage of development, as intramuscular injection of Kp1 has no effect on LH at the pubertal stage, while both Kp1 and Kp2 increase LH levels at gonadal recrudescence (919). In both sexes (adult immature stage) of the chub mackerel *Scomber japonicus*, icv administration of Kp2, but not Kp1, increases *fshβ* and *lhβ* mRNA levels (546, 547).

The role of Kiss was further investigated in knocked-out fish models. Two studies reported normal fertility in KO fishes for kisspeptin-related genes (zebrafish: (768); medaka: (524)). In KO medaka for *kiss1*, *kiss2*, *gpr54-1* or *gpr54-2*, ovaries and testes develop normally as compared to wild-type fish, with full-grown and late-vitellogenic follicles, and spermatozoa being observed, respectively (524). There are also no significant differences in the expression levels of both *lhβ* and *fshβ* between the kisspeptin-related gene KO lines and wild-type (524). Similarly, zebrafish with mutations for *kiss1*, *kiss2*, *kissr1* or *kissr2* show normal gametogenesis and reproductive capability, as well as normal expression levels of *gnrh2*, *gnrh3*, *lhβ* and *fshβ* (768). Double mutation (*kiss1*^{-/-}; *kiss2*^{-/-}), which prevents the compensation between ligands, causes lower expression of *gnrh3*, *lhβ* and *fshβ*, supporting that kisspeptin signalling stimulates the expression of these genes in zebrafish (768). However, these decreases had no impact on the phenotypes of the fish, as normal reproductive performance was reported (768). As compared to the induction of hypogonadotropic hypogonadism in mammals by loss-of-function mutation (human) or KO (mice) of *gpr54* or *kiss1* KO, these observations suggest a dispensable role of Kiss in the neuroendocrine control of reproduction in teleost models (zebrafish and medaka).

Interestingly, a study readdressed this question in mice by using ablation of kisspeptin neurons or of *gpr54*-expressing neurons (469). Differently from KO experiments, the authors

observed no impact on the timing of puberty, suggesting that kisspeptin neurons play a role in the optimization of reproductive success, by integrating various cues and relaying this information to GnRH neurons, but are dispensable for puberty onset, activation of GnRH pulses and fertility.

c- Loss of kiss function in birds?

As mentioned above (§ 5.2.3 a, b), phylogenomic studies suggest that two Kiss genes (*Kiss1* and *Kiss2*) have been inherited from the amniote ancestor. In the course of amniote evolution, *Kiss1* has likely been lost early in the bird lineage, while it has been conserved in some other sauropsids and in mammals. The existence of a *Kiss2*-like gene has been demonstrated in the genomes of several bird species, mallard duck, zebra finch, and rock pigeon (591). These avian *Kiss2*-like sequences diverge from those of other vertebrates and are not found in the genomes of chicken, falcon and parrot (591), revealing the processes of *Kiss2* gene pseudogenisation and loss in the avian lineage. Together with the loss of *Kiss1*, these results support the absence of any functional kisspeptin in birds. Concerning Kiss receptors, two genes (*KissR1* and *KissR4*) would have been inherited from the amniote ancestor. Synteny studies demonstrate the loss of *KissR1* in the bird lineage, but cannot conclude for the presence or not of *KissR4* with the current databases. Altogether, current phylogenomic analysis suggests the loss of *Kiss* genes in birds and a possible conservation or loss of a Kiss receptor (*KissR4*) (still to be found).

Immunocytochemical studies reported the presence of kisspeptin-like immunoreactive neurons in the medial preoptic nucleus of the hypothalamus in the mallard drake in close proximity to GnRH fibers and almost all these neurons co-express aromatase (658). This may correspond to the derived sequence identified in the duck even though the peptide mutations and the variations in gene structure suggest a pseudogenisation (591). Kisspeptin immunoreactivity is also observed in ovarian granulosa cells of hens (887), while genomic

and syntenic analyses support the loss of Kiss in this species (591). In goose, immunoreactive kisspeptin is also detected in the ovary (granular layer and theca of the follicle) and in the plasma where concentrations vary during the reproductive cycle (295). This raises the question as to whether the detection of immunoreactive kisspeptin in birds may result from cross-reactions with other RF-amide peptides.

A few functional studies using mammalian kiss peptides have been performed in birds. Central (icv) administration of kisspeptin-52 is able to increase plasma LH levels in the mallard drake, and pretreatment with a GnRH receptor antagonist prevented this increase in LH levels (658). Kisspeptin also increases plasma LH levels in the white-crowned sparrow (cited in (533)). However, in adult male chicken, human Kp-10 has an inhibitory effect, as intravenous injections of Kp-10 suppress plasma testosterone levels (847). Kisspeptin-10 treatment stimulates progesterone secretion in cultured chicken granulosa cells (887). Repeated injections of Kp-10 advance the initiation of egg-laying in the juvenile female quail (533) by increasing lipid synthesis as well as upregulating estrogen receptor protein and lipogenic gene expression in the liver (884). In the hypothalamus, Kp-10 induces an up-regulation of *cgnrh-I* expression and a down-regulation of *gnih* expression. In the pituitary, Kp-10 increases *lhβ* and *gnrh-rII* and decreases *fshβ* expression (533). Further studies are warranted to investigate whether these actions of heterologous kisspeptin in birds are mediated by a potential Kiss receptor (KissR4; still to be identified in birds) or by other RF-amide peptide receptors.

5.3.5. Kiss before vertebrates

In deuterostomes, in addition to vertebrates, two other sub-phyla constitute the phylum of chordates: the urochordates and the cephalochordates. Neither kisspeptin nor kisspeptin receptors have been found in urochordates (such as ascidians). In contrast, four kisspeptin-

type precursors and 16 kisspeptin-like receptors have been identified in the cephalochordate amphioxus *Branchiostoma floridae* (492), suggesting that multiple gene duplication events specifically targeted Kiss and KissR in this lineage. In *B. floridae*, one of the reported genes encodes three putative peptides, suggesting additional intra-gene duplication of peptidic sequences, while the other genes encode a single peptide (492). More recently, 27 putative KissR-like genes were identified in *B. floridae* (856). Further expression and functional studies were performed in the amphioxus *B. japonicum* on one kiss-like gene (*BjkissL-2*) and one kissR-like gene (*Bjgpr54L-1*) (856). Using qPCR and immunohistochemistry, the authors showed that *BjkissL-2* mRNA and protein levels are higher in notochord/nerve cord, and especially in the anterior region of the nerve cord (cerebral vesicle) and Hatschek's pit (856). *Bjgpr54L-1* expression is predominantly observed by qPCR in the notochord/nerve cord, moderate expression is seen in the testis and ovary, and lower expression in gill, muscle, hepatic caecum and hind-gut (856). Two amphioxus peptides show functional interaction with *Bjgpr54L-1*, while the receptor exhibits higher affinity for zebrafish Kiss peptides (856). Amphioxus synthetic Kiss peptides induce LH release in sexually mature female zebrafish and, in amphioxus, trigger the expression of *gpb5* mRNA, the glycoprotein subunit related to vertebrate glycoprotein hormones (see section 3), suggesting an ancestral role of Kiss-KissR in the neuroendocrine control of reproduction (856).

In non-chordate deuterostomes, echinodermata and hemichordata are sister phyla in a clade known as ambulacraria (285). The occurrence of kisspeptin-type receptors has been reported in ambulacrarian species, the sea urchin *S. purpuratus* (phylum echinoderms) and the acorn worm *Saccoglossus kowalevskii* (phylum hemichordates) (318, 492). Recently, kisspeptin-type precursors have also been identified in ambulacrarians, the starfish *Asterias rubens*, *S. purpuratus* and *S. kowalevskii* (694, 695). These precursors comprise two putative kisspeptin-like peptides.

Concerning protostomes, some kisspeptin-type receptors, but not yet a peptide precursor, have been found in lophotrochozoa (mollusca and annelida) (87, 318, 492). Precisely, kisspeptin-like receptors are present in mollusca, bivalvia (oysters, *Crassostrea gigas* and *Pinctata fucata* and mussel, *Mytilus galloprovincialis*) and gastropoda (limpet, *Lottia gigantea*; slug, *Aplysia californica*), as well as in annelida (worm, *Capitella teleta*) (87). The occurrence of kisspeptin-like receptors in lophotrochozoan invertebrates suggests the existence of kisspeptin-like peptides in these animals.

According to Elphick and collaborators, the evolutionary ancestry of kisspeptin-type receptors can be traced back to the common ancestor of the bilaterians, but with subsequent loss in urochordate deuterostomes and ecdysozoan protostomes (for reviews: (174, 175)). However, based on phylogenic and syntenic analyses using *Anopheles* mosquitoes (ecdysozoan), it appears that allostatin type A receptors (AST-ARs) and KissR emerged from a common gene ancestor after the divergence of galanin receptors (GALRs) in the bilaterian genome, suggesting that invertebrate AST-ARs and ligands shared a common evolutionary origin with vertebrate kisspeptin/galanin receptors and ligands (186).

5.3.6. Kisspeptin, more related to galanin/spexin than to other RF-amide peptides

Originally, the kisspeptin receptor was discovered for its high degree of sequence similarity with galanin receptors (396). Kim and collaborators found that spexin (*SPX*), galanin (*GAL*) and kisspeptin (*KISS*) genes are on the same reconstructed vertebrate ancestral chromosome (359). Their family genes are distributed among four 2R-generated paralogs (four linkage groups). Three linkage groups contain *SPX1* and *KISS2*, *SPX2* and *GAL*, and *KISS3* and galanin-like peptide (*GALP*), respectively. The fourth linkage group has *KISS1* alone. The ancestral forms of *KISS*, *GAL* and *SPX* are proposed to arise by local tandem duplications before 2R (Figure 9) and to expand their family members through 2R (359). Likewise, *KISSRs* and *GALRs* have probably emerged through local duplications before 2R, producing

three subgroups in vertebrates: KISSRs (4 KISSRs), GALR1 (GALR1a and GALR1b), and GALR2/3 (GALR2a, GALR2b and GALR3)(for review: (904). SP1 and SPX2 are functional ligands for GALR2 and GALR3 and are even more potent than GAL in activating GALR3 (359). The evolutionary origin of the KISS (*farp-4*)/SPX/GAL family is far distant from those of the NPFF (*farp-1*)/QRFP(*farp-3*) and PrRP(*farp-2*)/NPY families, so that some authors propose that kisspeptin should be classified separately (for review: (904)). This infers that common peptide sequences such as the C-terminal sequence shared by the RF-amide peptide super-family may reflect conservation but also convergences of peptide sequences especially suitable for bioactivity.

The galanin peptide family is constituted of galanin, galanin message-associated peptide (GMAP; encoded by the same gene as galanin), galanin-like peptide (GALP; encoded by a distinct gene) and alarin (encoded by a splice variant of GALP gene) (for review: (389)). Spexin (SPX; now renamed SPX1) was discovered in 2007 in human proteome (493). A second form, SPX2, has been characterized in all vertebrates except mammals (359). GALR2 and GALR3, but not GALR1, have been shown to be the cognate receptors for SPX (359). Regarding functional roles of these peptides, they share an involvement in the control of reproduction, especially as a link between metabolism and reproduction, which have been previously reviewed in depth by other authors (for reviews: galanin family, (182, 478); GALP, (393); spexin, (441)).

5.4. Prolactin releasing peptide (PrRP) group (*farp-2*)

The search for the ligand of the human orphan pituitary receptor, hGR3, led to the identification of a new peptide from bovine hypothalamic extract that acts as a prolactin-releasing factor in rat anterior pituitary cells and was thus named prolactin releasing peptide, PrRP (280). The prepro-protein generates at least two forms of mature peptide, PrRP31 and

PrRP20 (a C-terminal fragment of PrRP-31) (280)). At the same time, another RF-amide peptide, with a similar amino acid sequence, was isolated from the brain of a teleost, the Japanese crucian carp, and named Carassius-RFa (C-RFa) (210). C-RFa homologs have been characterized in other teleosts as well as in chicken, *Xenopus* and lamprey, but not in mammals, and C-RFa had been considered as a teleost PrRP (for review: (762)). However, while looking for PrRP and C-RFa in chicken, Wang et al (2012) found that PrRP and C-RFa are encoded by distinct genes in non-mammalian vertebrates, originating through duplication of an ancestral gene (386). Tachibana and Sakamoto (762) thus proposed that the widely used name of PrRP/C-RFa in lower vertebrate species be renamed PrRP2, as previously suggested by Wang and collaborators (859).

Data in non-mammalian vertebrates indicate that PrRP and C-RFa/PrRP2 are able to stimulate PRL release *in vitro* (teleosts: C-RFa in tilapia, (685); C-RFa in rainbow trout, (508, 646)) and *in vivo* (bird: comparison C-RFa et mPrRP, (763); amphibian: PrRP, (655); teleost: (508)). In contrast, after the initial finding of Hinuma and collaborators (280), other studies in mammals questioned the role of PrRP as a prolactin releasing factor and thus led to the hypothesis that this role of PrRP may be ancient and even lost in mammals. In fact, there is now clear evidence that PrRP is involved in the control of feeding behavior and energy expenditure in mammals as well as in other vertebrates (for reviews: (154, 762)).

Several studies support a role of PrRP in the neuroendocrine control of reproduction in mammals. Icv injection of PrRP to male rats increases plasma LH, FSH and testosterone levels (684), while icv administration of an anti-rat PrRP serum causes a reduction of LH surge (283). As PrRP is not able to induce release of LH and FSH directly from dispersed male pituitary cells *in vitro*, but instead can increase the release of GnRH from hypothalamic explants (684), it was suggested that PrRP could stimulate gonadotropin secretion *via* a hypothalamic mechanism involving the release of GnRH in male rat. The control of GnRH1

neurons by PrRP in rat is further supported by the presence of PrRP fibers in the medial preoptic area and of PrRP receptors in GnRH1 neurons (187). To the best of our knowledge, no data are yet available for such a role in other vertebrates.

Phylogenetic, pharmacological and paralogon analyses reveal that prolactin releasing hormone receptor (PrRP-R) shares a common ancestry with neuropeptide Y (NPY) receptors (385). In fact, NPY binds to PrRP-R1 and inhibits response of PrRP-R1-expressing cells to PrRP, behaving as an antagonist. NPY-type peptides have an ancient origin in bilaterians as they are present both in protostomes (328) and deuterostomes. An ancestral PrRP peptide probably started coevolving with a redundant NPY receptor, which then became PrRP-R, approximately 500 Million years ago (385). The distinct PrRP/NPY family genes and their receptor genes emerged by local gene duplication during early vertebrate evolution (for review: (904)) (Figure 9). NPY has been largely recognized for its involvement in the interactions between food intake, metabolism and reproductive function (for reviews: (146, 473, 519)).

5.5. Conclusion on RF-amide peptides

While RF-amide peptides, which all share a conserved C-terminal RF-amide signature, have been described as a family of neuropeptides encoded by five different genes in mammals, phylogeny and synteny analyses suggest that they do not all derive from a common ancestor and perhaps should not be seen as a family.

As reviewed above, RF-amide peptides, such as GnIH and kisspeptin, are critically involved in the control of reproduction and puberty. Most RF-amide peptides (GnIH, kisspeptin, QRFP/26RFa, PrRP) and non-RF-amide peptides which they are related to, such as NPY for PrRP and galanin/spexin for kisspeptin, are also major regulators of food intake and metabolism (for reviews: (153); GnIH, kisspeptin (848) ; kisspeptin (877) ; QRFP/26RFa

(404); PrRP (762) ; galanin, spexin (182, 441) ; NPY (519)), which can be closely linked to reproduction (452). Modulation of nociception is mainly exerted by NPFF and, to a lesser extent, by other RF-amide peptides such as QRFP/26Rfa (for reviews: (29, 404)).

Some data point out that RF-amide peptides display low selectivity toward the different RF-amide peptide receptors, within and between receptor families. Cross-activities between RF-amide peptides and their various receptors have notably been demonstrated *in vitro*. For instance, PrRP has high affinity, and higher efficacy than NPFF, at the NPFFR-2 receptor (178); 26Rfa interacts with a receptor distinct from GPR103 (26Rfa receptor) that may be NPFFR-2 (74); Kisspeptin-10 exhibits high binding affinity and receptor activation towards NPFFR-1 and NPFFR-2 (551). PrRP, kisspeptin and 26Rfa activate NPFFR-1 and NPFFR-2 and thus may modulate nociception (171).

Together, these data highlight the complexity of the diversification of neuropeptides and their receptors via local and whole genome duplications, conservation, losses and convergences, and the putative variety of interactions between multiple paralogs of ligands and receptors.

6. Non-peptidic neuromediators and the control of reproduction

6.1. Introduction

In addition to GnRH and some other peptides, non-peptidic neurotransmitters such as monoamines (catecholamines, indolamines and histamine), acetylcholine, and amino acids (glutamic acid and gamma-aminobutyric acid, GABA) may also play a more or less prominent role in the neuroendocrine control of reproduction (for reviews: (34, 222, 621, 840, 864, 875, 921)). This chapter will focus on the role of dopamine, norepinephrine, serotonin, histamine, and GABA in the control of reproduction.

6.1.1. Ancient, multifunctional neuromediators

In the nervous system of adult vertebrates, neurotransmitters act as chemical mediators of intercellular communication by the activation of specific receptors and second messengers in postsynaptic cells. This specialized role appears to have evolved from more ancestral functions in primitive organisms where these substances were used as both intra- and intercellular signals. Indeed, a number of 'classical' neurotransmitters are present in primitive organisms and early embryos in the absence of a nervous system (79) and it has been suggested that these molecules “initially functioned as intracellular regulators, then became local hormones, and finally acquired the role of synaptic transmitters” (80, 811).

It is now clear that in vertebrates, that most known central nervous system neurotransmitter substances may also participate in the regulation of pituitary secretion and that in some instances “neurotransmitters” behave like releasing hormones. The best example is dopamine (DA) which, in mammals, is released from nerve endings of tuberoinfundibular DA (TIDA) neurons in the median eminence and pituitary stalk to activate DA receptors at the pituitary level after being transported there by portal blood vessels. Hence, the definitions of neurotransmitters and neurohormones are partially intermingled (810). Neurotransmitters can participate in the control of pituitary secretion by serving as a neurotransmitter input, or releasing factor output, of hypothalamic neuroendocrine transducer cells; they can act also within these cells, or act as neurotransmitter within a nerve tract that impinges upon the hypothalamus (23).

a- Monoamines

Monoamines (such as catecholamines, serotonin, histamine) are evolutionary ancient molecules. They are present in metazoa and also in some protozoa (811). They control neural and endocrine systems in both non-vertebrates and vertebrates. In vertebrates, physiological and pharmacological evidences make it clear that monoamines are involved in the regulation of anterior pituitary hormone secretion, including gonadotropins (LH and FSH).

2119 -The catecholamines, dopamine (DA), norepinephrine (NE) and epinephrine (E) are major
2120 neurotransmitters found in most, if not all, metazoan species, although the nature of the
2121 catecholamines may differ between animal phyla. Their role as neuromediators or
2122 neurohormones is documented in a limited number of species: While the neuromodulatory
2123 functions of DA appears to be conserved in all bilaterians (505), that of NE is clearly
2124 demonstrated only in vertebrates. In mammals, both have been implicated in the regulation of
2125 GnRH secretion (222, 339).

2126 -The indoleamine, serotonin (5-hydroxytryptamine; 5-HT), first identified as a
2127 neurotransmitter-signaling molecule in mammals, is ubiquitous across all forms of life. Cells-
2128 containing 5-HT have been found in representatives from all major metazoan clades, *e.g.*,
2129 cnidarians, plathyhelminths, nematodes, arthropods, annelids, mollusks, echinoderms,
2130 tunicates and vertebrates (30, 137, 268) suggesting an early appearance during animal
2131 evolution. As regards reproductive functions, various studies in vertebrates have
2132 demonstrated a role of 5-HT in the secretion of reproductive neurohormones and sexual
2133 behaviors (for review (621)).

2134 -Histamine (HA): Classically established as a “peripherally” important mediator of
2135 inflammation, HA is now accepted to play a role in neurotransmission (254). The brain
2136 histaminergic system is a phylogenetically old group of neurons that project to most regions
2137 of the central nervous system (253).

2138 b- GABA

2139 GABA (gamma amino butyric acid) is known as the main inhibitory neurotransmitter in the
2140 brains of mammals (144). Such a function appears ancestrally derived, as GABA exerts
2141 similar inhibitory functions in the nervous system of even the most primitive animals (238).
2142 GABA plays a key role in the control of pituitary hormone release, including gonadotropins,
2143 in mammals (414, 839) as in fish (799).

2144
2145 6.1.2. Non-peptidic neuromediators produced via enzymatic synthesis: phylogeny of enzymes
2146 to retrace their evolutionary history

2147 Nonpeptidic neuromediators are decarboxylated derivatives of amino acids: DA and NE are
2148 synthesized from tyrosine, 5-HT from tryptophan, HA from histidine, and GABA from
2149 glutamic acid, in one or more enzymatically catalysed reactions of which the first serves as
2150 the rate-limiting step.

2151 a -Aromatic Amino acid hydroxylases (AAAH)

2152 The first step in catecholamine and indoleamine biosynthesis is the ring hydroxylation of the
2153 aromatic amino acid substrates (tyrosine or tryptophan respectively) catalysed by a class of
2154 rate-limiting enzymes, the aromatic amino acid hydroxylases (AAAH). These proteins belong
2155 to a family of tetrahydrobiopterin (BH₄)-dependent monooxygenases, which in vertebrates
2156 includes one phenylalanine hydroxylase (PAH), two tyrosine hydroxylases (TH1 and TH2)
2157 and two tryptophan hydroxylases (TPH1 and TPH2).

2158 AAAHs are present in phylogenetically distant taxonomic groups such as bacteria, insects and
2159 mammals (85). The TH, TPH, and PAH genes are found in all sequenced genomes of
2160 bilaterians, supporting the presence of each of the AAAH family members long before the
2161 divergence of chordates (595). Phylogenetic studies suggest that the AAAHs originated by
2162 duplication and divergence of a common ancestral gene at the base of the eukaryotic tree.
2163 Some lineage-specific intron loss or gain events have occurred during the expansion of
2164 AAAH genes and generated diversity of gene structures (85). The high level of sequence
2165 identity between different subfamilies suggests evolutionary conserved functions.

2166 In eukaryotes, these enzymes are composed of a homologous central catalytic domain to
2167 which is attached discrete N-terminal regulatory domains and a short C-terminal
2168 tetramerization domain, whereas the bacterial enzymes lack the N- and C-terminal domains.

Therefore it is believed that the C-terminal portions of all three enzymes arised from a common ancestor, and represent the catalytic core (243) while the amino terminal regions are responsible for substrate specificity. The eukaryotic hydroxylases are all homotetramers (see (195, 773).

-TH catalyzes the hydroxylation of tyrosine to L-dihydroxyphenylalanine (L-DOPA), the first and rate-limiting step in the biosynthesis of catecholamine neurotransmitters DA, NE and E (409). Two paralogous genes encoding TH are found in teleost fishes, amphibians, birds and non-eutherian mammals. They emerged as a consequence of a WGD which occurred before the divergence of jawed vertebrates (probably 2R-WGD), but TH2 was secondarily lost in eutherian mammals (893). The history of TH gene evolution within vertebrates may be also shared by the other AAAH (893).

-TPH catalyzes the hydroxylation of tryptophan to 5-hydroxytryptophan, the first and rate-limiting step in the biosynthesis of serotonin (321). Two distinct molecular isoforms of TPH, TPH1 and TPH2, resulting from a whole genome duplication (WGD) which occurred in the vertebrate lineage, are present in the brains of zebrafish (44) as well as humans, mice and rats (851). The TPH isoform discovered first is referred to as TPH1 and is primarily found in the pineal gland of mammals (243, 421). By contrast, the second TPH isoform, TPH2 first cloned from the rat pineal gland (139) is strongly expressed in 5-HT-producing neurons of the raphe nucleus in mammals (593, 851), and also of the hypothalamus in teleosts (632). Sequence homology analysis of vertebrate TPHs indicates that the sequence identity between TPH1 and TPH2 within a species is low, whereas the sequence identities between TPH1s or TPH2s from different species are relatively high. While two TPH genes (*tph1* and *tph2*), are found in most groups of jawed vertebrates, in teleost fishes (for instance, in zebrafish, stickleback and medaka) three paralogs (*tph1a*, *tph1b* and *tph2*) that likely result from the teleost-specific whole genome duplication (TWGD), have been described (for review (421)).

b- Amino acid decarboxylases (ADC)

The aromatic amino acid decarboxylase (AADC), also called DOPA decarboxylase, is encoded by the *ddc* gene, and transforms L-DOPA into DA. AADC also transforms 5-HTP into 5-HT. AADC is a member of the large family of decarboxylases which include other enzymes involved in the synthesis of neurotransmitters, such as histidine decarboxylase (HDC) for histamine and glutamate decarboxylase (GAD) for GABA (651). HDC is highly conserved throughout metazoa (254). AADC is present in both protostomes and deuterostomes, suggesting its presence in ancestral bilaterians. AADC has been duplicated in insects leading to two paralogous genes (*ddc* and *amd*). In mammals, alternative splicing generates various *ddc* transcripts, one being specific to the nervous system (894).

Glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamate, the (*single and*) rate-limiting step in the biosynthesis of GABA. Throughout the vertebrate taxa, GAD exists as two major isoforms, GAD65 and GAD67 (for review (799)). They are thought to derive from 2 paralogous genes that arose in early vertebrates at least in a gnathostome ancestor as both GAD65 and GAD67 paralogs have been cloned from two chondrichthyan species; in contrast a single GAD appears to be present in non-vertebrate chordates, urochordates (ascidians) and cephalochordates (amphioxus) in which the GAD sequence are highly divergent (70, 391). There is also evidence for a third GAD gene in a teleost, the armoured grenadier, although this paralog does not classify with either GAD 65 or 67. It is found throughout the grenadier brain including the hypothalamus but its importance there remains unexplored (799).

6.1.3. Origin and evolution of neuromediator receptors: direct phylogeny

Neurotransmitter receptors are critical elements in intercellular signaling within the central nervous system and are divided into two major types, based on their molecular structure and biophysical properties.

a- G-protein-coupled receptors (GPCRs)

Most of, if not all, the physiological actions of catecholamines, indolamines and histamine, as well as some actions of GABA (via GABA_B receptors) are mediated by receptors which belong to the largest membrane protein family known so far, the seven transmembrane (7-TM) segment receptors coupled to heterotrimeric G-protein (G-protein-coupled receptors or GPCRs). This family of receptors transmits the effect of agonist binding to the various intracellular effectors by interacting with an intermediary G-protein (532). The diversity of receptor subtypes inside this neurotransmitter receptor superfamily, observed in many animal species, is the result of a long and complex evolutionary process consisting in gene duplications and continuous accumulation of mutations. GPCRs are believed to have evolved through a series of gene duplication and divergence events that started with a single ancestral gene (209): the first event was the divergence of the catecholamine receptors from the muscarinic acetylcholine receptors, which occurred prior to the divergence between deuterostomes and protostomes, since they are present at least in arthropod and vertebrate lineages. Subsequently, the ability to activate specific second-messenger pathways diverged independently in both the muscarinic and the catecholamine receptors (209).

The calculation of phylogenetical distances between bioamine receptors revealed two main periods of diversification: the first one likely occurred in the Precambrian before the separation between the protostomes and deuterostomes and corresponds to the appearance of the main subtypes of bioamine receptors. The second one, might have accompanied the cephalization of the CNS in vertebrates (836).

b- Ligand-gated ion channels

Ligand-gated ion channels, also called ionotropic receptors, are transmembrane ion-channel proteins, which after binding of their ligands, allow the passing through of permeant ions (such as sodium, potassium, chloride and calcium), leading to changes in membrane potential. This superfamily of proteins is found in almost all forms of life (238), with strong structural similarities despite the variety in ions gated and in ligands (850). Two subtypes of GABA receptors (GABA_A and GABA_C) and the subtype 3 of serotonin (5-HT₃) receptors are members of this superfamily. They are composed of five homologous subunits. Evolutionary scenario of the family of GABA_A and glycine-like receptors (GLR), suggests the presence of an ancestral receptor in bilateria and that a set of local gene duplications, WGD rounds in early vertebrates (1 R and 2 R) and gene loss led to current set of GLR subunits in extant vertebrates including human (803).

6.2. A key-neuromediator: dopamine

6.2.1. Major brain neuromediator in human and other mammals

Dopamine (DA) is a neurotransmitter broadly distributed in the vertebrate central nervous system (CNS) (311). After its discovery as a neurotransmitter in the CNS of vertebrates ((88, 89), DA has raised large interest for its various roles in brain functions and its involvement in severe human pathologies. DA systems regulate sensory perception, motor function, memory, emotion, food intake, and various hypothalamic functions including the neuroendocrine control of pituitary hormones. Pathologies related to the multiple functions of DA include Parkinson's disease (291), schizophrenia, Tourette Syndrome, addiction to drugs, and pituitary adenoma (for reviews (63, 311, 681)). The involvement of DA in diverse brain functions is ensured by independent dopaminergic systems (894).

a - Multiple brain dopaminergic systems; multiple brain functions; multiple receptors

2266 The dopamine systems in vertebrates are highly diversified anatomically and also molecularly
2267 as regards DA biosynthesis enzymes and receptors. Gene duplications and losses have
2268 contributed to this diversification (891–893). The mammalian brain contains ten
2269 neuroanatomically distinct dopaminergic systems (named A8 to A17) located in the forebrain
2270 and midbrain (64). The (A8-A10) DA neurons are involved in initiation of movement and
2271 behavioral responses as well as in drug addiction. The A11 DA neurons are involved in
2272 autonomic motor regulation, and the A12-A15 neurons in neuroendocrine regulation. The
2273 A16 DA cell bodies in the olfactory bulb and A17 in the retina are involved in olfactory and
2274 visual perceptions, respectively (63, 64, 724). Comparative anatomical and functional studies
2275 highlight both conservation and divergences of DA forebrain and midbrain systems across
2276 vertebrates (345, 724, 894).

2277 The pleiotropic activity of DA also relies on a diversity of receptors. DA exerts its actions on
2278 target cells by activating specific membrane receptors belonging to two structurally and
2279 functionally different classes of GPCRs, termed D1 and D2, and originally distinguished by
2280 their ability to activate (D1 class) or inhibit (D2 class) adenylate cyclase (351). D1 and D2
2281 receptors also regulate other signal transduction pathways including calcium and potassium
2282 channels and arachidonic acid synthesis [reviewed in (314, 494, 712, 828)]. D1 and D2
2283 receptors both belong to the group A (rhodopsin-like) of the GPCR superfamily but have
2284 different structural features. D1 receptor genes are intronless, and D1 receptor proteins exhibit
2285 a short third cytoplasmic loop and a long C-terminal tail. They are coupled to the Gs family of
2286 G proteins, and D1 receptor agonists promote adenylyl cyclase activity. In contrast, D2
2287 receptor genes contain several introns and encode a long third cytoplasmic loop and a short C-
2288 terminal tail. D2 receptors are coupled to the Gi/Go family of G proteins, and D2 receptor
2289 agonists inhibit adenylyl cyclase activity.

Each class of DA receptors comprises two to five subtypes depending on the vertebrate species: in mammals, the D1 class comprises two receptor subtypes (D1 and D5), while the D2 class comprises three receptor subtypes (D2, D3 and D4). However, in non-mammalian species, additional DA receptor genes have been found. Phylogenetic analyses strongly suggest that the common ancestor of Osteichthyans possessed four subtypes in the D1-class (D1, D5, D6 and D7), and five subtypes in the D2-class (D2, D3, D4, D8/D2_l and D9/D4_{rs}; (891, 892). While multiple gene losses have largely reduced the number of DA receptors in mammals, many DA receptor genes have been conserved in other vertebrates; moreover, teleost-specific WGD (3R) further increased the number of DA receptor genes in this lineage (891).

Notably, D1 and D2 DA receptors are phylogenetically not more related to each other than to other monoamine receptors (82, 131, 892). This suggests that the ability to bind DA, shared by the two receptor classes, was acquired independently reflecting a convergence process during metazoan evolution.

b- Neuroendocrine functions (e.g. major inhibitory regulator of pituitary prolactin via dopamine D2 receptors)

In mammals, DA represents the major nonpeptidergic agent exhibiting well-defined neuroendocrine functions and its role as an inhibitor of pituitary lactotroph cell secretion became recognized in the 1970s: based on the evidence of dopaminergic nerve terminals in the median eminence (215), McLeod and coworkers (445) proposed that DA may be released into the pituitary portal system, and thereby act as a hypothalamic hormone (distinct from its neurotransmitter role in other systems). They demonstrated that dopaminergic agonists were effective at suppressing prolactin (PRL) secretion *in vivo*, and *in vitro* from isolated pituitary glands (445). DA was subsequently detected in the pituitary portal blood (340), and variations of DA levels in the portal blood were shown to account for changes in PRL secretion in

various physiological conditions (47, 48, 229, 242). DA receptors of the D2 class were identified on anterior pituitary lactotroph cells (453). Finally, the observation that mice lacking the DA D2 receptor are hyperprolactinemic (352, 652), clearly demonstrated the critical role of DA in suppressing endogenous PRL secretion. Interestingly, in all hormonal systems studied so far, whether at the hypothalamic, posterior pituitary, or anterior pituitary level, DA functions as an inhibitor via DA receptors of the D2 class (for reviews (46, 241)). While DA is now established as the primary regulator of PRL gene expression and release in both mammals and teleost fish (46, 241, 872), it also exerts some negative control on the release of growth hormone (GH), thyroid-stimulating hormone (TSH) and melanocyte-stimulating hormone (α -MSH) (for review (810)) in the pituitary of both mammals and teleost fish, despite differences in the neuroanatomical organization of the hypothalamo-pituitary axis between these vertebrate classes (32). An additional neuroendocrine action of DA, initially discovered in teleosts and later demonstrated in various vertebrate species, is the inhibitory control of gonadotropin secretion and reproductive function ((168, 603); see section 6.2.4).

6.2.2. Evolution of tyrosine hydroxylase, key-enzyme of dopamine synthesis

a- Biosynthetic pathway of dopamine

Dopamine is synthesized from the aromatic amino acid tyrosine through two enzymatic steps. The first and limiting step is catalyzed by an aromatic amino acid hydroxylase (tyrosine hydroxylase [TH]), and the second step by the aromatic amino acid decarboxylase (AADC), often called DOPA-decarboxylase. TH, as the other AAAHs, has at least one homolog in all bilaterian species studied so far. TH probably evolved from an ancestral AAAH that did not have a regulatory domain and gave rise to all three present-day AAAH (394).

b- Tyrosine hydroxylase 1 and 2 in vertebrates

The gene coding TH has been identified in species of several vertebrate groups, including humans (521), rats (244), mice (301), bovines (136), quails (184), chicken (90) and lamprey (35). Whereas only one gene encodes TH in mammals (with two to four proteic isoforms generated by alternative splicing), two non-allelic TH genes (th1 and th2) exist in several teleost species (84). Phylogenetic analyses showed that both th1 and th2 genes are not only found in teleosts but also in all studied non-eutherian vertebrates, therefore in all vertebrates except placental mammals (893). It is thus likely that the ancestral vertebrates possessed TH1 and TH2 DA-synthesizing cells.

The existence of two paralogous TH genes in teleost fishes, amphibians, birds and non-eutherian mammals suggests that the gene duplication giving rise to the two TH genes is ancient in the vertebrate lineage (35) probably as a consequence of the second round (2R) of WGD (548, 575, 713). While TH2 is still found in prototherian (platypus) and metatherian mammals (opossum), it may have been lost in the eutherian mammalian lineage which possess a single TH, TH1 (893). Genomes of many eutherians are fully sequenced, and the chromosomal localizations of the TH genes and their syntenic genes support the loss of TH2 in the eutherian mammals. Indeed, apart from the absence of TH2 in the eutherian mammals, the order of the neighbouring genes (IGF1, PAH, and ASCL1) at the locus is highly conserved.

c- Tyrosine hydroxylase in metazoa

Tyrosine hydroxylation, and its regulation, is an ancient and critical biochemical pathway. The hydroxylation of tyrosine to form L-3, 4-dihydroxyphenylalanine is an enzymatic pathway utilized not only throughout animal phyla but in plants as well. TH, as the other AAAH, has at least one homolog in all bilaterian species studied so far (505).

The gene coding TH has been identified from various species of non-vertebrates, including schrimps (454), fresh water crab (*D pagei*; (615)), parasitic helminthes (*Schistosoma mansoni* (258); *Schistosoma japonicum* (294), and insects, [*Drosophila* (760); moth (300); cricket (862)]. In several species of insects, as in mammals, different isoforms of TH produced by alternative splicing have been identified (in the cricket (862), in *D. melanogaster* and the armyworm *M. separata* (62, 534). Since the drosophila TH protein exhibits similar kinetic parameters and regulatory mechanisms to its mammalian counterpart, it is likely that very strong evolutionary constraints have been placed on the biochemical mechanism (529).

6.2.3. Evolution of Dopamine D2 receptors

The D2 receptors have been diversified as a consequence of genome duplications in early vertebrates. In mammals, three DA receptors (D2, D3 and D4) are classified as the D2 class. The classification and nomenclature of DA receptors has been initially based on the set of receptors found in eutherian mammals. When more DA receptors have been found in other groups of vertebrates, the necessity of revisiting DA receptor classification was raised by some authors (147, 891, 892).

a- Impact of WGD

The number of DA receptors subtypes has been multiplied by the two major rounds (1R/2R) of WGD that took place in early vertebrates (286, 296, 438). Additional duplication of DA receptor gene occurred in the teleost fish lineage *via* TWGD (3R) (15, 316, 617, 772). Duplicated paralogous genes were maintained in some vertebrate groups, probably by the acquisition of some differential functional properties, specific of each subtypes, as well as by discrete changes in their expression patterns in the brain (for reviews (861,862)).

b- Multiple genes in teleosts

Five subtypes of D2 receptor genes (*D2*, *D3*, *D4*, *D8* (also named *D2_l* for *D2_{like}*) and *D9* (also named *D4_{rs}* for *D4- related sequence*) exist in teleosts. The *D2_l* and *D4_{rs}* genes would have originated in the ancestor of gnathostomes (562). Phylogenetic analyses strongly suggest that the ancestral Osteichthyes (bony jawed vertebrates) possessed five D2-class of DA receptors (*D2*, *D3*, *D4*, *D8* and *D9*) likely resulting from 1R/2R with a possible additional specific duplication (891, 892). In eutherian mammals, only three D2-class DA receptors are found (*D2*, *D3*, *D4*) due to multiple DA receptor gene loss in this lineage (891). In contrast, up to seven D2 class DA receptors (*D2a*, *D2b*, *D8*, *D3*, *D4a*, *D4b*, *D9*) have been identified in the zebrafish (66, 67, 891), the additional receptors (*D2a*/*D2b*, *D4a*/*D4b*) likely resulting from TWGD.

6.2.4. Dopamine as a major inhibitory regulator of gonadotropin secretion in teleosts

A major neuroendocrine action of DA, initially discovered in teleosts and later demonstrated in various vertebrate species, is the inhibitory control of gonadotropin secretion and reproductive function (167, 168, 603). This inhibitory role of DA appears to be a powerful counterpart to the well-known stimulatory role of GnRH in the neuroendocrine control of reproduction.

a- Discovery in goldfish

The discovery by Peter and colleagues, using brain lesion approaches, of the presence of a gonadotropin release-inhibiting factor (GRIF (604)) in the hypothalamus of goldfish has been previously reviewed (167). GRIF neurons were subsequently shown to originate from the preoptic area (POA) and project to the pituitary (606). *In vivo* experiments aimed at investigating the effect of various DAergic agonists and antagonists on LH secretion and ovulation strongly suggested that DA could be the GRIF (100). Immunocytochemical and neuroanatomical studies supported this conclusion by revealing DA cell bodies in a specific

region of the POA, the nucleus preopticus anteroventralis (NPOav), with projections in the proximal pars distalis of the pituitary where gonadotrope cells are located (333, 606). Lesions of the NPOav induce a surge of LH and subsequent ovulation (336). Finally, *in vitro* studies on primary cultures of goldfish pituitary cells revealed that DA inhibits both basal and GnRH-stimulated LH release by acting directly on gonadotropes, through binding to receptors pharmacologically-related to the mammalian D2 receptors (101). In addition, in goldfish, DA exerts inhibitory effects on GnRH neurons, blocking the synthesis of the peptide or its release from the pituitary nerve terminals (602, 901). The discovery of a dual control of reproduction led to a major application in aquaculture: the development of a spawning induction method based on combined treatments with a DA antagonist and a GnRH agonist that has been widely used to induce spawning in captivity of a certain number of species (LINPE method, named after the scientists R. Peter and HR Lin (for review (603))).

b- Evidence in various teleosts

As a matter of fact, the role of DA as a GRIF, originally demonstrated in the goldfish, a cyprinid, has been later on observed in various other teleost species, including other cyprinids, but also in species belonging to other teleost subgroups such as silurids, salmonids, percomorphs, mugiliforms, elopomorphs (for review (167)) and pleuronectiforms (251).

In some teleost species, however, this physiological role of DA was not found (for review (168)). It is worth noting that the intensity of the dopaminergic inhibition varies according to the species, from a drastic barrier in cyprinids (603, 605) or in prepubertal eel (166, 837) to a milder control in salmonids (659).

As in the goldfish, DA actions on gonadotrope cells are mediated by receptors of the D2 class in all species studied (European eel (326, 838), tilapia (408) catfish (26), grey mullet (10) and zebrafish (202)). In zebrafish, ISH and ICC studies reveal that the TWGD-paralogs D2a and D2b as well as D8 are expressed in LH-producing cells, suggesting that the three receptors are

involved in mediating DA inhibitory control in this teleost (202). In the eel, the TWGD-paralog D2b is predominantly expressed as compared to D2a in LH and FSH cells (326). The expression of D2a and D2b is differentially regulated by sex steroids (585) and the two receptor subtypes are differentially involved in the onset of puberty (319). These data suggested a functional differentiation of the TGWD-D2 paralogs in the eel, with a major role of the D2b receptor in the control of gonadotropic function (326).

6.2.5. Dopamine as an inhibitory regulator of gonadotropic axis in other vertebrates

A dopaminergic inhibition of GnRH-induced pituitary gonadotropin secretion has also been found in a chondrostean fish, the white sturgeon (*Acipenser transmontanus*; (596)). This indicates that the role of DA in the inhibitory control of reproduction may have a more ancient evolutionary origin, in an actinopterygian ancestor, common to teleostean and chondrostean fishes.

The inhibitory influence of DA on gonadotropin secretion and reproduction is not restricted to fish (584, 837): A dopaminergic inhibitory control of reproduction has been shown also in representative species of various other classes of tetrapods as demonstrated in amphibians, birds, and mammals (for review (168)).

In amphibians, some data point to an important role for dopaminergic inhibition in the regulation of seasonal reproduction. In the frog, *Rana temporaria*, lesions of the infundibular hypothalamus in hibernating preovulatory females cause advanced ovulation (734, 735). This effect is mimicked by a dopaminergic antagonist and blocked by administration of a dopaminergic agonist (736). More recent studies indicate that the inhibitory effects of DA on reproduction are conserved in frogs: for instance, in the wood frog, injection of quinpirole in females delays or inhibits oviposition (844). The release of sperm and eggs is induced in several anurans and salamanders by the co-injection of a GnRH agonist and the selective DA

receptor D2 antagonist metoclopramide (termed “the amphiplex method” (121, 240, 795, 796, 845). The technique has also been successfully applied in small-scale trials to several other amphibian species (796).

In birds, there is similar evidence for an inhibitory role of DA on reproduction (for review (168)). For instance, in laying hens, the anovulatory state induced by food withdrawal, is caused by a dopaminergic inhibition of GnRH release at the median eminence level, where a dense concentrations of DA and GnRH-containing processes is observed, providing opportunities for synaptic interactions between them (128).

In mammals, DA is involved in the modulation of pulsatile LH release in some species. This effect has been extensively studied in seasonal mammals notably in sheep, in which DA participates in the inhibition of gonadotropic activity before puberty (73) as well as in adults during seasonal anestrus (for reviews (221, 781)) by acting on GnRH neurons at the median eminence level (379), through D2 receptors (55). In rat, GnRH neurons are directly innervated by catecholamine terminals, including DA ones (106), but the participation of the dopaminergic system in the control of FSH and LH release remains controversial in adults since raising brain DA activity can either inhibit (41, 130, 222, 432) or stimulate (412, 444) gonadotropin release. By contrast, in the developing rat, DA clearly exerts an inhibitory control on both LH and FSH secretion during the second and third weeks of female life, by influencing GnRH release into the portal blood (384). In some other species, a direct inhibitory effects of DA on LH release at the pituitary level has been reported: for instance, in rabbits, DA injected intravenously inhibits GnRH- stimulated LH secretion in normal and also in stalk-sectioned animals (138). Finally, in humans, several observations suggest that a direct inhibition by DA on LH release may occur under physiological and pathological conditions. For instance in men, infusion of DA (which does not cross the blood-brain barrier) significantly decreases circulating LH levels and attenuates the LH release in response to a

bolus of GnRH (299). This DA-induced inhibition of LH secretion is associated with a reduction in both pulse frequency and amplitude of LH secretion. Further, the observation that partial inhibition of LH secretion occurs even in the presence of constant GnRH and DA infusion suggests that DA may also modulate the gonadotrope response to GnRH. In women with functional hypothalamic amenorrhea (FHA), a reduction of LH pulse frequency (and of PRL concentrations) has been documented, which can be reversed by a DA receptor blocker. In this case, however, a hypothalamic site of DA action was inferred, through inhibition of GnRH pulse frequency (52).

Recently, in male and female mouse, DA has been shown as the most potent inhibitor of GnRH neuron excitability: using a variety of electrophysiological approaches, the authors demonstrated that approximately around half of all GnRH neurons are inhibited by DA through D1 and D2 receptors, and that the inhibition exerted by DA on GnRH neurons is independent on gonadal steroid status (430).

In summary, DA acts as an inhibitor of reproduction in representatives of all classes of vertebrates, but this role has been differentially conserved throughout vertebrate evolution. This may either reflect an ancient regulatory pathway, common to actynopterygian (chondrosts and teleosts) and sarcopterygian (tetrapods) species, or result from convergent recruitments of DA neurons for the inhibition of reproduction in various vertebrate taxa (167). The recruitment of DA neurons for exerting similar functions in different vertebrates suggests that DA neurotransmission may be especially suitable for the neuroendocrine inhibitory control of reproduction.

6.2.6. Dopamine as an inhibitor of reproduction in other metazoan

The inhibitory role of DA in the control of reproduction may be more ancient than the origin of vertebrates. Indeed, a few studies have reported an inhibitory action of DA on reproductive function in some non-vertebrate species. For example, DA inhibits the growth and maturation of oocytes in an echinoderm, the sea urchin *Strongylocentrotus nudus* (358). It is thus likely that this control was present in the ancestor of deuterostomes. In protostomes, an inhibitory effect of DA on reproduction has been reported both in some ecdysozoans (such as insects, crustaceans, nematodes) and lophotrochozoans (such as mollusks). In insects, DA levels are constantly maintained at a high level in the hemolymph during diapauses (308, 537, 538), and change with the photoperiod (115). In particular, DA is clearly a key factor for the induction of egg diapause of the silkworm, *Bombyx mori* (537). In crustaceans, there is evidence for a dopaminergic inhibition of testicular maturation in the fiddler crab, *Uca pugilator* (666) and in the red swamp crayfish, *Procambarus clarkii* (668). Similarly, in the giant freshwater prawn, *Macrobrachium rosenbergii*, DA inhibits testicular maturation (711) and inhibits vitellogenin synthesis and ovarian maturation by inhibiting the release of vitellogenesis-stimulating hormone (VHS) from the thoracic ganglia (107, 787). In a nematode, *Caenorhabditis elegans*, genetic and pharmacological analyses reveal that a dopaminergic pathway, acting through a D2-like DA receptor (755), inhibits egg laying (865). In a mollusk, zebra mussel, DA has been shown to reduce the intensity of 5-HT-induced spawning (199). It is thus likely that inhibitory actions of DA on reproductive functions occurred in the bilaterian ancestor and even possibly predate the emergence of bilateria, since even in a cnidarian, the coral *Acropora tenuis*, DA was reported to have an inhibitory effect on spawning (310). Therefore, although its physiological functions appear to differ among species, DA plays multiple roles in suppressing the reproductive events in a number of non-vertebrate species (Figure 12).

2537

2538 **6.3. Many other neuromediators involved in the control of reproduction**

2539 A variety of actors in mammals: Among neurotransmitters, that have been reported to also
2540 influence LH release and play a role in the control of reproduction, are found NE, 5-HT, HA
2541 as well as GABA.

2542

2543 **6.3.1. Norepinephrine (NE)**

2544 **a- In mammals**

2545 Sawyer and colleagues gave the first evidence that noradrenergic neurons may participate in
2546 the control of the gonadotropic axis, by demonstrating that α -adrenergic receptor antagonist
2547 blocks ovulation in rabbits (676). Further studies by various laboratories reported that NE
2548 may modulate plasma LH levels by regulating the activity of GnRH neurons (for review (34).
2549 However, the idea that NE was essential for triggering of the preovulatory release of LH (34)
2550 has been challenged by experiments in rodents (120, 675), and in primates (369, 376),
2551 showing that chronic interruption of the noradrenergic afferents to the hypothalamus does not
2552 impair normal ovulation. This strongly suggests that the noradrenergic system, far from being
2553 essential, exerts a modulatory action on gonadotropin secretion. It is now accepted that NE
2554 has a permissive action within the network of afferences to GnRH neurons, which may be
2555 modulated by sex steroid levels (275).

2556 **b- In other vertebrates**

2557 The role of NE in the control of reproduction has also been investigated in other vertebrates.
2558 In birds, existing evidence suggests a role for NE in the neuroendocrine control of LH release.
2559 The avian median eminence is known to be well supplied with NE fibers and terminals (81,
2560 701), and the α -adrenoreceptor blocking drug, dibenamine, has been early shown to
2561 suppresses ovulation in the hen (786). Specific blockade of NE synthesis prevents ovulation

in the laying hen (867) and causes a decline in plasma concentrations of LH in young and adult male domestic fowl (75, 76). *In vitro*, GnRH secretion from chicken hypothalamus-preoptic area slices (410) or from Japanese quail hypothalamus explants (486) is significantly elevated in the presence of NE or β adrenergic agonists. However, icv administration of NE in laying and non-laying turkeys has no effect on LH secretion (262). In non-laying geese, noradrenergic stimulation is involved in the control of LH secretion, probably through GnRH neurons (897). In the Chinese geese (*Anas cygnoides*), the expression of DBH (the enzyme catalyzing the transformation of DA into NE) undergoes marked periodic variations in reproductive and endocrine tissues during the reproductive cycle (890). In the Japanese quail, a noradrenergic pathway is involved in the control of LH release through a modulation of GnIH gene expression in the hypothalamus (789).

In teleosts, NE appears to play only a slight stimulatory role on gonadotropin secretion, by acting either directly on gonadotrope cells, via α_1 -like adrenergic receptors (98) or on hypothalamic GnRH neurons to stimulate the release of GnRH (607, 902). In fish, as in mammals, the effectiveness of NE is dependent on the stage of gonadal development: *e.g.* in goldfish, NE stimulates LH release mainly during gonadal regression (98, 603).

c- In other metazoa

Few data are available on the role of NE in the reproductive function in other metazoa. In mollusks, cyclic variations of NE strongly support its participation in the reproductive cycle of bivalve species. Notably, marked variations in NE content occur in the gonads and pedal ganglia of mussels, with a 3 to 4-fold increase during gametogenesis and a decline during spawning (368). Similarly, increased NE levels are measured in gonad of the female Pacific lion's paw Scallop during gametogenesis stages (developing and maturing stages) while NE concentrations drop after spawning, suggesting that NE exerts a direct control over gametogenesis (433).

Collectively, data reveal the recruitment of NE signalling in the control of reproduction both in protostomes in deuterostomes, as well as in cnidaria, before the emergence of bilateria. (Figure 12).

6.3.2. Serotonin (5-HT)

a- In mammals

There is strong pharmacological evidence for a role of 5-HT in the regulation of hypothalamo-pituitary-gonadal axis, through an action either on GnRH neurons or on gonadotrope cells. Actually, 5-HT neurons located in the raphe region may play inhibitory roles in gonadotropin secretion: the pharmacological elevation of hypothalamic 5-HT levels with monoamine oxidase inhibitors suppress spontaneous ovulation in rats (383) and *in vitro*, 5-HT significantly inhibits the release of GnRH from the mediobasal hypothalamus of male rats (Charli et al, 1978). In sheep (155) and rabbits (624), infusion of 5-HT into the mediobasal hypothalamus blocks the ovulatory discharge of LH and ovulation. On the other hand, several lines of evidence support a permissive or facilitatory role for 5-HT in ovulation: inhibition of 5-HT synthesis with PCPA, suppresses ovulation in rats (383) and several 5-HT antagonists inhibit spontaneous ovulation (457).

Actually, the hormonal environment of the animal appears to be critical to the expression of 5-HT actions on gonadotropin secretion and ovulation. Indeed, 5-HT system can be modulated by gonadal steroids (222, 515, 598) and in several mammalian species, 5-HT receptors are colocalized with estrogen receptors beta (250), indicating that 5-HT and reproductive endocrine signaling pathways are closely associated. Accordingly, differential effects are observed in male and female rats: neonatal exposure to androgen is responsible for the sex difference in the LH response to 5-HTP, a 5-HT precursor, a difference which may be associated with a regulatory action of 5-HT on the cyclic hypothalamic control of

gonadotropin secretion (501). 5-HTP has been shown to stimulate FSH release in normal rats and to inhibit it in castrated rats, testosterone concentration being a relevant factor in determining the 'type' of effect produced (331).

The functional interactions between 5-HT and reproductive functions have also been demonstrated in other vertebrates:

b- In other vertebrates

In birds, 5-HT synthesized in the hypothalamus exerts an inhibitory influence on reproduction: elevation of 5-HT levels directly inhibits GnRH synthesis and LH secretion in female turkey (256) or hen (657) and male domestic fowl (257). Conversely, blockade of the serotonergic system generally stimulates gonadotropin secretion and enhances gonadal development, as shown in young female turkeys (256), or in aging male roosters (27).

In teleosts, by contrast to what is observed in birds, hypothalamic 5-HT neurons exert a positive stimulatory influence on reproductive neuroendocrine function and gonadotropin secretion (for review (621)). Specifically, 5-HT stimulates GnRH release, LH release and socio-sexual behaviors, acting at different levels. At the hypothalamic level, a close association of 5-HT fibers with GnRH neurons has been observed in the Atlantic croaker (354). However, central administration of 5-HT has no effect on preoptic GnRH1 mRNA levels (782), indicating that 5-HT may stimulate GnRH release but not synthesis. As a matter of fact, 5-HT stimulates GnRH release from the hypothalamus of the goldfish and seabream (696, 902). In the zebrafish, 5-HT receptors are present in several regions containing GnRH neurons (539) suggesting possible expression of 5-HT receptors in GnRH neurons, as in mammals (56).

At the pituitary level, in several teleost species, 5-HT stimulates gonadotropin release *in vivo* and *in vitro* (goldfish (730, 731, 878); Atlantic croaker (353, 355)). In some other teleost species, 5-HT alone has no influence on spontaneous LH release, but potentiates GnRH

2637 analog-induced LH secretion when co-administered (Atlantic croaker (878); Prussian carp
2638 (729)). Interestingly, the stimulatory action of 5-HT on GnRH release is time- and season-
2639 dependent (355), and the mode of action of 5-HT on gonadotropin release also changes as a
2640 function of the reproductive stage: in the Atlantic croaker, the effect of 5-HT is more
2641 pronounced in mature than in sexually regressed fish (353).

2642 Therefore, as in mammals, the stimulatory action of 5-HT on gonadotropin secretion in teleost
2643 appears to be modulated by various factors such as gonadal steroids, environmental
2644 conditions and social cues (for review (621)).

2645 c- In other metazoans

2646 Together with DA and NE, 5-HT represents a possible endocrine and neuronal link between
2647 endogenous and exogenous signals allowing non-vertebrates to modulate reproductive
2648 functions in conjunction with environmental constraints (368). In non-vertebrates, the
2649 function and location of 5-HT have been studied mainly in arthropods, mollusks and annelids.
2650 In crustaceans, 5-HT is involved in various physiological processes including sexual behavior
2651 and reproduction (191, 666, 668, 669, 711). Specifically, 5-HT stimulates release of gonad
2652 stimulating hormone (GSH) in the crayfish *Procambarus clarkia* (668) and in the fresh water
2653 crab (620) and also accelerates testicular maturation in the fiddler crab (666, 667) and the red
2654 swamp crayfish (668) as well as ovarian maturation and spawning in the white shrimp (827).

2655 In several species of mollusks, 5-HT and its receptors play an important role in reproduction,
2656 through stimulation of biosynthesis and release of active egg-laying peptide precursor
2657 proteins, *i.e.* control and initiation of gamete release, and gamete maturation. For instance,
2658 studies on bivalves show that 5-HT levels change during the different stages of the sexual
2659 cycle (resting, developing, maturing and egg-laying) in the gonads and cerebroid ganglia of
2660 mussels, and that the endocrine function of gonads in marine bivalves is regulated through
2661 monoamine neurosecretions arising from the cerebroid ganglia (368). Moreover,

administration of 5-HT induces oocyte maturation and spawning (282, 466, 766). The endogenous 5-HT signal is transmitted to the oocyte through 5-HT receptors (33, 857). In annelids such as Nereidae, immunopositive staining for 5-HT is observed in neurons of the brain of *Nereis diversicolor* (278) and 5-HT exerts a positive effect on oocyte development, probably by stimulating a gonadotrophic hormone, present in mature females (392). Altogether these studies indicate a conserved or convergent role of 5-HT in the control of reproduction in various bilateria, protostomes and deuterostomes (Figure 12). The presence of 5-HT receptors has been demonstrated in cnidarian, thus before the emergence of bilateria (for review (860)), but to our knowledge the effect of 5-HT on reproduction in this phylum has not yet been addressed.

6.3.3. Histamine (HA)

The possible stimulatory effect of histamine (HA) on LH secretion was first evidenced in the rabbit by Sawyer (674) who reported that icv injection of HA induces ovulation and increases plasma LH levels in animals lightly anesthetized with pentobarbital but not awake or ether-anesthetized. Subsequent studies, however, provided inconsistent results, likely depending on sex steroid environment: icv injection of HA increases plasma LH levels in proestrous or ovariectomized estrogen and progesterone-primed female rats (157, 160, 418), but has no effect in males (156, 158). Actually, HA participates in the neuroendocrine regulation of pituitary hormone secretion by an indirect action at a hypothalamic level: In mammalian brain, HA cell bodies are located exclusively in the tuberomammillary nucleus (TMN) of the posterior hypothalamus (253) and send their axons all over the central nervous system. In the hypothalamus they arborize extensively and may thereby influence the release and function of various hypothalamic neuropeptides and hormones (254), including GnRH (368, 395):

GnRH-induced secretion of LH in female rats (497). By contrast, it does not affect LH release from isolated rat pituitary cells (57) or pituitary fragments (497).

Considering the ancient origin of HA, investigation on its potential role on reproductive function in other vertebrates and other metazoa would deserve to be launched.

6.3.4. GABA

GABA is an inhibitory neurotransmitter extremely abundant in the brain of all vertebrates, that plays a role in the control of reproduction in various vertebrate classes.

a- In mammals, the influence of GABA on LH secretion has long been demonstrated (21, 159, 388, 560, 839). The distribution of hypothalamic GABAergic neurons and their involvement in the neural control of reproductive processes are now well documented (451). Although both GABA_A and GABA_B receptors have been identified in rat pituitary gonadotrope cells (21) and that evidence exists for a possible direct stimulatory effect of GABA on the LH cells (842), the vast majority of studies support a key inhibitory role of GABA on gonadotropin release, predominantly at the central level, through modulation of the GnRH neuron activity and secretion. Notably, increasing endogenous GABA concentration by drugs, GABA or GABA agonist administration, in rats and non-human primates, prevents ovulation and pulsatile LH release, and blunts the LH surge induced by estrogen or an estrogen-progesterone combination (162). GABA infusion into the preoptic area or intraperitoneal injection of muscimol, a GABA_A receptor agonist, blocks the LH surge (7, 277), while the GABA_A receptor antagonist, bicuculline, advances the timing of the LH surge (363). Moreover, GABA release in the preoptic area decreases prior to and during the time of the LH surge (317).

GABAergic activity is known to be sensitive to environmental conditions (183) and the alteration of GABAergic neuronal activity is likely associated with the season-dependent

reproductive cyclicity in seasonal mammals (235). GABAergic activity may also depend on the stage of reproductive development: in female mice, at puberty, the effect of GABA on GnRH neurons switches from depolarization to hyperpolarization ((259). Both autoradiographic and immunohistochemical studies show that a large proportion of GABA neurons in the diencephalon represents targets for estrogens (197, 277, 388, 471), and it has been postulated that these neurons may mediate estrogen feedback on GnRH neurons, (388, 752), as suggested by the existence of synaptic contacts between GABAergic terminals and GnRH neurons (405, 733). Interestingly, it appeared recently that a subpopulation of GnRH neurons in the adult mouse forebrain is GABAergic and thus that GnRH neurons could secrete GABA to regulate their own activity (917).

GABA exerts its regulatory effects via two main receptors, the GABA_A and GABA_B subtypes. The origin and evolution of the GABA receptors is highly complex. As some publications exist, focusing on the phylogeny of the multiple GABA_A receptor (458, 650, 803), this topic will not be addressed in the present review.

In vivo experiments undertaken in adult rats, sheep and monkeys all indicate that the inhibitory effect of GABA on LH secretion is mediated through the GABA_A receptors located on the soma of GnRH neurons (276, 277, 495, 683). Furthermore, GnRH neurons express functional GABA_A receptors that may inhibit GnRH neuronal excitability (260, 717, 743). Much less is known about the possible involvement of GABA_B receptors. Functional GABA_B receptors are present in various hypothalamic neurons (11, 12, 387, 846) but studies examining their role suggest that major species differences exist. In the ewe, GABA_B receptors mediate inhibition of GnRH secretion during the non-breeding season, but not during the breeding season, this change being possibly part of the mechanism for the seasonal shift in the negative-feedback effect of estradiol on LH secretion (683). In the adult rat, GABA_B receptors play an important role in controlling the excitability of GnRH neurons

especially in females (429). Interestingly, GABA stimulates GnRH secretion in the adult rat (59, 161). Yet, the precise physiological role of the excitatory action of GABA on GnRH neurons remains elusive (861).

b- In other vertebrates

In birds: The domestic turkey is a seasonally breeding bird with a reproductive cycle regulated by photoperiod and terminated by the state of photorefractoriness (720). In this bird, GABAergic neurotransmission in the hypothalamic premammillary nucleus regulates reproductive seasonality and the onset of photorefractoriness (374) through GABA_A receptors (374).

In teleost fish, there is also good evidence for the involvement of GABA in the control of LH release (451, 799, 921). Following the discovery of a heavy GABAergic innervation of the anterior pituitary in goldfish, (334, 335), the effects of GABA have been explored, mainly in goldfish (for review (616)), and to a lesser extent in trout *Oncorhynchus mykiss*. By contrast to its inhibitory effect in mammals, GABA predominantly stimulates LH secretion in adult goldfish and trout, although inhibitory actions have been described in two other species, the Atlantic croacker (356) and the common carp (116).

In goldfish, intraperitoneal injection of GABA increases serum gonadotropin levels (338). Injection of a GABA transaminase inhibitor, that augments GABA levels within the hypothalamus and pituitary, also induces an increase in serum gonadotropin levels (723). This stimulatory effect of GABA on gonadotropins can be accounted for by two major mechanisms: stimulation of GnRH secretion (338, 723) and inhibition of DA release (723, 797, 798) at the brain level. *In vitro*, GABA also induces a dose-related stimulation of GnRH release from pituitary slices, which in teleosts contain GnRH nerve terminals (797). By contrast, GABA does not directly stimulate LH release from dispersed goldfish pituitary cells *in vitro* (338). The *in vivo* stimulatory effect of GABA varies seasonally and is modulated by

sex steroids (338, 356, 459, 798). Both muscimol (a GABA_A receptor agonist) and baclofen (a GABA_B receptor agonist) stimulate LH secretion in females, indicating that both receptor subtypes may mediate the effect of GABA (459, 799).

In rainbow trout, GABA exerts an overall stimulatory effect on basal and GnRH-induced LH, but also on FSH secretion, both *in vivo* and *in vitro*, and these effects are also highly dependent on the sex and the reproductive stage of the fish (451). As in mammals and goldfish, a role for GABAergic neurons as target cells for oestrogen feedback on LH release has been hypothesized in rainbow trout because oestrogen receptors are present in GABAergic, but not in GnRH neurons. In addition, the stimulatory action of GABA may also be exerted directly onto the gonadotrope cells of the pituitary, as GABA stimulates basal and GnRH-induced FSH and LH secretion from dispersed pituitary cells (451).

In the zebrafish brain, the connection between GABAergic and GnRH neurons has been recently evidenced: GnRH3 neurons are directly contacted by GABAergic neurons in the ventral telencephalon and hypothalamus (733). Moreover, as shown also in mouse (917), some GnRH neurons in the anterior part of the telencephalon coexpress GAD67, thus being also GABAergic. Administration of GABA_B receptor agonists and antagonists support the implication of GABA_B receptors in the regulation of GnRH neurons (733).

In agnaths, studies in sea lamprey also indicate that GABA may directly affect GnRH release in the brain: dual-label *in situ* hybridization shows that GABA cells are closely apposed to GnRH cells in the rostral hypothalamus and preoptic region (647). *In vitro* perfusion or *in vivo* injection of GABA and its analogs both significantly increase GnRH in the brain (647), suggesting that GABAergic control of GnRH is phylogenetically ancient.

c- In other metazoa

GABA may also play some role in the control of reproduction in other metazoa: for instance, GABA induces spawning in non-chordate deuterostomes, echinoderms (764). GABA also

enhances reproduction in protostomes such as rotifers (220), indicating a role of GABA in the control of reproduction in both deuterostomes and protostomes. The presence of GABA receptors demonstrated in cnidaria, attests the early origin of GABA receptors before the emergence of bilateria (for review (346)), and should inspire future investigation on the possible role of GABA in reproduction of basal metazoa (Figure 12).

6.4. Neuromediators and reproduction: from conservation to disruption

6.4.1. Ancient origin of neuromediators and receptors in metazoan

The neurotransmitter function of DA, NE, 5-HT, HA and GABA in adult organisms is their more recently developed function. Cell communication through secreted, diffusible signals is phylogenetically older than neural transmission (223), and the substances known as neurotransmitters appeared long before the development of the most primitive nervous system and even multicellular organisms (79): Organisms like protists and animals devoid of nervous system, as sponges and placozoans, produce a wide array of molecules, which are in some cases identical to the corresponding compounds found in higher taxa (223). Monoamines (catecholamines, indoleamines and HA) are found in many protozoans and in almost all metazoans (811). Non-bilaterian metazoans, with or without neurons, exhibit many components of the molecular toolkits for synapse function. GABA, catecholamines, and indoleamines as well as a large number of G protein-coupled receptors for monoamines, and biogenic amine-synthesizing enzymes can be found in prebilaterian animals such as cnidarians (69). GABA is used as a signal molecule by non nervous cells of vertebrates (224) and also in sponges (173) and in plants (71).

The catecholaminergic signalling has an old phylogenetic history and the enzymatic pathway for the biosynthesis and degradation of monoamine transmitters and the β -adrenergic-mediated mechanisms were conserved throughout evolution from early metazoans to

2811 mammals (223). Alpha-adrenergic receptors are found in representatives of two major clades
2812 of bilateria, the protostomes and the deuterostomes (40).

2813 If we take the example of monoamines, according to Turlejski hypothesis (811): their
2814 “*earliest role has been as intracellular regulators of cell activity*”. Produced either inside the
2815 cell or entering it from its environment, they act directly on some of the intracellular signaling
2816 systems, and “*cause long-lasting changes in the cell functional state, that allow the organism*
2817 *to adapt to its environment*”. “*However, very early in evolution, they acquired functions of*
2818 *hormones*”, *i.e.* molecules of external origin acting on specific receptors localized in the cell
2819 membrane and stimulating specific intracellular second messengers to cause long-term
2820 changes in the functional state of cells. “*Later on in evolution, biogenic amines acquired*
2821 *functions of neuromodulators*”, thus produced and released by specific neurons, and able to
2822 modulate the activity of other neurons, through specific receptors placed within synaptic
2823 contacts. “*Finally, preserving some of the evolutionary older functions, monoamines took the*
2824 *function of neurotransmitters conveying fast changes*”, through receptors activating ion
2825 channels (811).

2826 The development of a signaling system requires the evolution of a mechanism for producing
2827 signals, receptors and adaptive reactions to the signal. Various data now support the
2828 evolutionary model proposed by Harris and Zahavi (263) to explain the selection of these
2829 precise molecules for intercellular communication: « Classical neurotransmitters » are small
2830 molecules that are catabolic products of biological molecules involved in basal cell
2831 metabolism: DA and NE are produced from tyrosine, 5-HT from tryptophan, HA from
2832 histidine, GABA from glutamate,... and the extracellular release of these molecules reflects
2833 the metabolic activity of the secretory cell. Their (i) physico-chemical characteristics, which
2834 are best suited to display reliably the levels of specific metabolic activities, and (ii) toxicity
2835 which induced the selection by neighboring cells of membrane proteins to bind them, may

explain why they have been selected for paracrine communication and then for nervous communication (263).

6.4.2. Non-peptidic neuromediators as potential targets for neuroendocrine disruption of reproduction: a phylogenetic approach

Neuroendocrine disruptors (NEDs) are defined as “*pollutants in the environment that are capable of acting as agonists/antagonists- or altering the synthesis and/or metabolism- of neuropeptides, neurotransmitters or neurohormones, which subsequently alter diverse physiological, behavioral or hormonal processes to affect an animal's capacity to reproduce, develop and grow, or deal with stress and other challenges*” (863).

While NEDs are now well known to adversely affect reproduction through binding to steroid receptors (mimicking or antagonizing the activity of steroid hormones), it is important to mention that they may also affect reproductive functions by acting upon neurotransmitter systems (such as DA, GABA, NE and 5-HT) that modulate GnRH output (150, 400). To take only a few examples in mammals: (1) bisphenol A (BPA): When pregnant rats are orally administered BPA, the turnover of DA and 5-HT in the forebrain are accelerated in both the mother and the offspring, suggesting an increase in the release of both monoamines from nerve endings (288). BPA exposure, at even lower doses than environmentally relevant levels, was shown to have a great impact on monoamine levels in neonatal rat brain over 28 d after its disappearance (463). In male mice, an increase in anxiety-like behavior induced by perinatal exposure to BPA seems to be related to decreases in DA metabolites and in the activity of monoamine oxidase (MAO)-B in the brain. (462). (2) Polychlorinated biphenyls (PCBs), that are industrial chemical products, also affect DA and 5-HT levels in the brain: they have been shown to bind to 5-HT, DA, and NE receptors (689). Decreased brain levels of DA, DOPAC and HVA are observed in the brain of pregnant rats treated with PCBs, but also

in the brain of their offspring (289). PCBs and brominated flame retardants (BFRs) decrease DA turnover, primarily via inhibition of DA transporters DAT and VMAT, and also decrease the uptake of glutamate and GABA, inhibiting GABA signaling, and decreasing 5-HT levels. Several epidemiological studies have shown that PCBs and BFRs may be responsible for similar effects in humans (for review (200)). (3) GABAergic neurons in the preoptic area of the rat brain are known targets of TCDD, a dioxin, and may mediate developmental effects of this contaminant on reproductive function (270).

In birds also, several hypothalamic neural systems proved to be responsive to NEDs (571–573): for instance, there is evidence in the quail that the catecholamine and indoleamine systems may be altered by perinatal exposure to NEDs (571).

In fish (for review (863)) various pollutants have been shown to impact neurotransmitters involved in the neuroendocrine control of reproduction. For example, (a) the antidepressant fluoxetine (FLU), one of the most prevalent environmental pharmaceutical contaminant in North American and European aquatic ecosystems, that is a selective 5-HT reuptake inhibitor (SSRI), was reported to affect multiple neuroendocrine pathways and behavioral circuits in teleost fishes including disruptive effects on reproduction (481). Recently, in zebrafish embryos, in very much the same as in mammals, FLU was shown to impair the serotonergic, dopaminergic and adrenergic neurotransmission systems at environmentally relevant concentrations, by down-regulating transcription patterns of monoamine receptors and transporters (134). (b) PCBs disrupt the stimulatory 5-HT/GnRH pathway controlling LH secretion activity by inhibiting hypothalamic TPH and decreasing 5-HT availability in croakers (357). (c) Mercury, both in its inorganic and organic forms, is capable of impairing the monoaminergic neurotransmitters involved in the regulation of GnRH and gonadotropins: after mercury exposure, 5-HT concentrations are decreased in the brains of several fish species, whereas levels of NE and DA are increased (for review (133)). (d) Pulp and paper

mill effluents contain compounds that interact with key enzymes and receptors that regulate the GABAergic, glutamatergic and dopaminergic modulation of GnRH and LH, thereby impairing reproduction in the goldfish (39). (e) Bifenthrin (BF), a pyrethroid insecticide, alters dopaminergic function in zebrafish embryos and juveniles (54).

While most investigations on NEDs are carried out with vertebrate models, research on non vertebrate species led to similar results: For instance, (i) in insects, azadirachtin (AZA), an insecticidal limonoid with antifeeding and sterilizing properties, blocks neurosecretion from the corpus cardiaca, interacting with the cholinergic, GABAergic and 5-HT systems (504). (ii) In crustaceans, cadmium and mercury have inhibitory effects on ovarian maturation in the red swamp crayfish, partly by inhibiting 5-HT-stimulated gonad-stimulating hormone release, and preventing the ovaries from responding to this hormone (633). Antidepressants, by interfering with 5-HT, DA or NE neurotransmission, affect freshwater amphipod activity patterns, marine amphipod photo- and geotactic behavior, and daphnid reproduction and development (for review (198)). (iii) In mollusks, in the freshwater mussel, exposure to estrogenic chemicals present in municipal effluents alters the normal metabolism of 5-HT and DA, both of which are involved in sexual differentiation (217). Antidepressants affect spawning and larval release in bivalves and reduce fecundity in snails. Exposure to the environmental contaminant, serotonergic antidepressant fluoxetine, induces spawning in estuarine and freshwater bivalves (for review (198)).

6.4.3. The “One Health concept”

The neuroendocrine systems, as the links between the brain and peripheral endocrine systems, play key roles in the ability of an organism to respond to its environment. They are thus highly vulnerable to disruption by environmental contaminants such as industrial chemicals, pesticides, pharmaceuticals..., the worldwide presence of which is now demonstrated. NEDs

are known to exert some of their adverse effects acting directly upon neurotransmitter pathways that regulate the neuroendocrine systems.

As most neurotransmitter molecules, as well as some of their receptors and transporters are phylogenetically ancient and conserved within the animal phyla, NEDs may interact with them and affect the neurotransmission systems of all metazoan. Chemical disruption of neuromediator signaling may therefore adversely affect health and reproduction in human but also in a diversity of wildlife thus encompassing the whole ecosystem.

In conclusion, molecular families of neuromediators, hormones, their biosynthesis enzymes and their receptors, involved in the neuroendocrine control of vertebrate reproduction, have an ancient origin in metazoa, pre-existing the emergence of vertebrates and the innovation of the brain-pituitary axis (Figure 13). Evolutionary scenarios, based on phylogeny approaches, enable retracing the origin and evolution of these molecular families, highlighting the impacts of gene and genome duplications, as well as gene loss events. Combined with physiological data they allow inferring evolutionary constraints and mechanisms leading to functional conservation and diversification of the actors of the neuroendocrine control of reproduction.

Call Out Box

- Reproduction is the essential biological process of living organisms and is therefore submitted to strong evolutionary constraints.
- In human as in other vertebrates, reproduction is controlled by the brain-pituitary gonadotropic (BPG) axis. Evolutionary endocrinology contributes to a better understanding of the neuro-endocrine control of reproduction in living organisms including human, by providing new insights on the origin, conservation and variations of the key actors of the BPG axis.

- As revealed by molecular phylogeny analyses, many actors that have been recruited for the BPG axis in vertebrates (neuromediators, neurohormones, hormones, biosynthesis enzymes, and receptors) belong to large molecular families of an ancient origin in metazoa.
- The number of actors of the BPG axis has expanded *via* the two rounds of whole genome duplication that occurred at the basis of the vertebrate lineage, which is at the origin for instance of the two gonadotropins LH and FSH and their sister hormone the thyrotropin TSH. Local gene duplications have also contributed to an increase of actor numbers, and such is the origin of human chorionic gonadotropin.
- An additional round of whole genome duplication has occurred at the basis of the teleost fish lineage, so that some “fish models” currently used for biomedical research, such as zebrafish or medaka, may present a larger number of actors as compared to human.
- Conversely to gene increase via duplications, gene loss events have also marked the evolutionary history of some BPG actor families, as is the case for kisspeptin receptors, with a single gene left in human, as compared to four in basal vertebrate representatives.
- The synthesis and function of the BPG axis actors (neuromediators, neurohormones and hormones) are the targets of disruption by environmental pollutants from industrial, agricultural and pharmaceutical activities. The ancient origin of the BPG actor families makes a variety of living organisms both targets and sentinels of neuro-endocrine disruption. This highlights some of the strong links between ecosystems, biodiversity health and human health, within the framework of the “OneHealth” concept.

Acknowledgements. The authors thank Dr Anne Gaëlle Lafont for her contribution to figure drawings.

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Figure Legends

Figure 1. Neuroendocrine control of reproduction in mammals: the brain-pituitary-gonad axis. Internal and environmental factors are integrated at the brain level and modulate the activity of gonadotropin-releasing hormone (GnRH) neurons. GnRH is released in the hypophyseal portal vessel system and controls the production of pituitary gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), which in turn control gonad activity. A variety of neuromediators, peptidic and non-peptidic, are also involved in the control of GnRH and gonadotropins, such as Kisspeptin (Kiss), gonadotropin-inhibiting hormone (GnIH), dopamine (DA), norepinephrine (NE), serotonin (or 5-hydroxytryptamine 5-HT), Histamine (HA), gamma-aminobutyric acid (GABA). The pituitary gland, as a relay between brain neurons and peripheral glands is considered as a vertebrate innovation.

Figure 2. Vertebrate phylogeny with a special focus on whole genome duplications.

Two rounds (1R and 2R) of whole genome duplication (WGD) occurred at the basis of the vertebrate lineage. Whether the 2nd round occurred before or after (doted line) the emergence

of the cyclostome lineage is still under debate. A third round (3R) of WGD occurred specifically in the teleost lineage, and is also referred to as TWGD (teleost-specific whole genome duplication). Human belong to mammalian, amniote, tetrapod, sarcopterygian lineages. Coelacanth is a representative species of basal sarcopterygians. Actinopterygians are the sister clade of sarcopterygians.

Figure 3. Metazoan phylogeny.

Human belong to the vertebrate, chordate, deuterostome, bilateria lineages. Urochordates are considered as the sister clade of vertebrates. Among bilateria, protostomes are the sister clade of deuterostomes. The most consensual classifications of protostomes distinguish two sister clades, lophotrochozoa and ecdysozoa. Cnidaria represent one of the basic groups of metazoa.

Figure 4. Schematic representation of the glycoprotein hormone (GpH) α and β subunits and comparison with predicted GPA2 and GPB5 structures.

Amino acids are represented by circles. Glycosylation chains are represented by Y shape sign. Position of intron splicing sites is indicated by V shape sign. The disulfide bonds are symbolized by bars, red bars between red circles for those responsible for the cystine-knot structure and in grey for the additional ones. The conserved cysteine residues are numbered. Location of the β strands (β 1- β 4) and loops (L1-L3) is indicated.

Figure 5. Schematic representation of the gene duplication, genome duplication and gene loss events leading to the extant repertoire of glycoprotein hormone subunit related genes in vertebrates.

1R, 2R: first and second rounds of whole genome duplication in early vertebrates; 3R: third round of whole genome duplication in early teleosts. 1* The GPA2-GPB5(a) tandem was

maintained in teleosts and basal sarcopterygian (coelacanth). GPB5a was lost in tetrapods. 2* Thyrotropin $\beta 2$ subunit (TSH $\beta 2$) was maintained in basal sarcopterygians (coelacanth, lungfish) and chondrichthyes but lost in teleosts and tetrapods. 3* The LH β subunit encoding gene was duplicated in primates to generate several copies of the chorionic gonadotropin β (CG β) subunit genes. 4* After 3R, except for the TSH $\beta 1$ subunit, only one of the duplicated glycoprotein hormone related genes was conserved. 5* Some teleosts may have two copies of the GPH α subunit resulting from recent, specific tetraploidization events.

Figure 6. Evolutionary scenario of the GnRH family in vertebrates (adapted from (219)).

Anc GnRH: ancestral gonadotropin-releasing hormone gene. 1R, 2R: first and second rounds of whole genome duplication in early vertebrates; 3R: third round of whole genome duplication in early teleosts. Black cross: gene loss. Red arrow: local gene duplication.

Figure 7. Evolutionary scenario of the GnRH receptor family in vertebrates (adapted from (644)).

Anc GnRHR: ancestral gonadotropin-releasing hormone receptor gene. 1R, 2R: first and second rounds of whole genome duplication in early vertebrates; 3R: third round of whole genome duplication in early teleosts. Black cross: gene loss. Red arrow: local gene duplication.

Figure 8. Two evolutionary scenarios of the GnRH-like systems in bilaterians (adapted from (654)).

Anc: ancestral; GnRH: Gonadotropin-releasing hormone; CRZ: corazonin. AKH: adipokinetic hormone; ACP: AKH/corazonin-related peptide. Black cross: gene loss. Red arrow: local gene duplication.

Figure 9. Evolutionary relationships between RF-amide and non RF-amide peptide families.

RF-amide peptides are encoded by 5 distinct genes in mammals, which have been named by Dockray (153) *farf-1* to 5, based on the chronology of their discoveries. Various nomenclatures are used according to authors and phyla such as: Neuropeptide F (NPFF) or PQRf for *farf-1*; Prolactin-releasing peptide (PrRP) for *farf-2*; Gonadotropin-inhibiting hormone (GnIH) or Neuropeptide VF (NPVF) or LPXFR for *farf-3*; Kiss for *farf-4*; QRFP or 26RF for *farf-5*.

The figure displays some current hypotheses on their evolutionary relationships (for reviews: (359, 567, 807, 904)):

NPFF (*farf-1*) and GnIH (*farf-3*) would be the closest related RF-amide peptide families, likely having a common PQRf ancestor and resulting from one of the two rounds of whole genome duplication (1R/2R WGD) that occurred in early vertebrates.

QRFP (*farf-5*) would be related to NPFF (*farf-1*) and GnIH (*farf-3*) families via a local gene duplication of their common ancestor, before the WGD duplication of NPFF and GnIH.

PrRP (*farf-2*) and Kiss (*farf-4*) would be more related to non RF-amide peptide families than to the other RF-amide peptide families: PrRP to neuropeptide Y (NPY) and QRFP to galanin and spexin, via local gene duplications, respectively.

Figure 10. Evolutionary scenario of the Kiss family in vertebrates (adapted from (587)).

Anc Kiss: ancestral Kisseptin gene. 1R, 2R: first and second rounds of whole genome duplication in early vertebrates; 3R: third round of whole genome duplication in early teleosts. Black cross: gene loss.

Figure 11. Evolutionary scenario of the Kiss receptor family in vertebrates (adapted from (587)).

Anc KissR: ancestral Kisseptin receptor gene. 1R, 2R: first and second rounds of whole genome duplication in early vertebrates; 3R: third round of whole genome duplication in early teleosts. Black cross: gene loss.

Figure 12. Ancient origin of neuromediators involved in the neuroendocrine control of reproduction.

Various neuromediators such as Dopamine (DA), norepinephrine (NE), serotonin (or 5-hydroxytryptamine, 5-HT), histamine (HA), gamma-aminobutyric acid (GABA) are involved in the brain control of reproduction in mammals. Their presence in other vertebrates, in other deuterostomes, in protosomes and in cnidaria (non-bilateria), suggests an ancient origin in metazoa. They may also have exerted an early role in reproduction in metazoa. Straight letters: neuromediator with a reported role in the control of reproduction. Italic letters with question mark: neuromediator present but no information on its putative role in reproduction.

Figure 13. Schematic drawing of the origin of some major actors of the brain-pituitary control of mammalian reproduction.

The pituitary gland is a vertebrate innovation ensuring the relay between the brain and peripheral glands and target organs. Molecular families of the various actors of the vertebrate brain-pituitary reproductive neuroendocrine axis have an ancient origin, largely preceding the emergence of the vertebrate lineage. Local and whole genome duplications in vertebrates contributed to the diversification of the Kiss and GnRH (Gonadotropin-releasing hormone) systems and of the glycoprotein (GP) hormones, pituitary gonadotropins FSH and LH, and chorionic gonadotropin CG. 1R, 2R: first and second rounds of whole genome duplication in

5836 early vertebrates; 3R: third round of whole genome duplication in early teleosts. Red bar:
5837 local gene duplication.

5838

5839 **Table legends**

5840 **Table 1. Sequences of GnRH-like peptides**

5841

**Environmental
factors**

Brain

Kiss
GnIH

DA, NE, 5-HT, HA
GABA

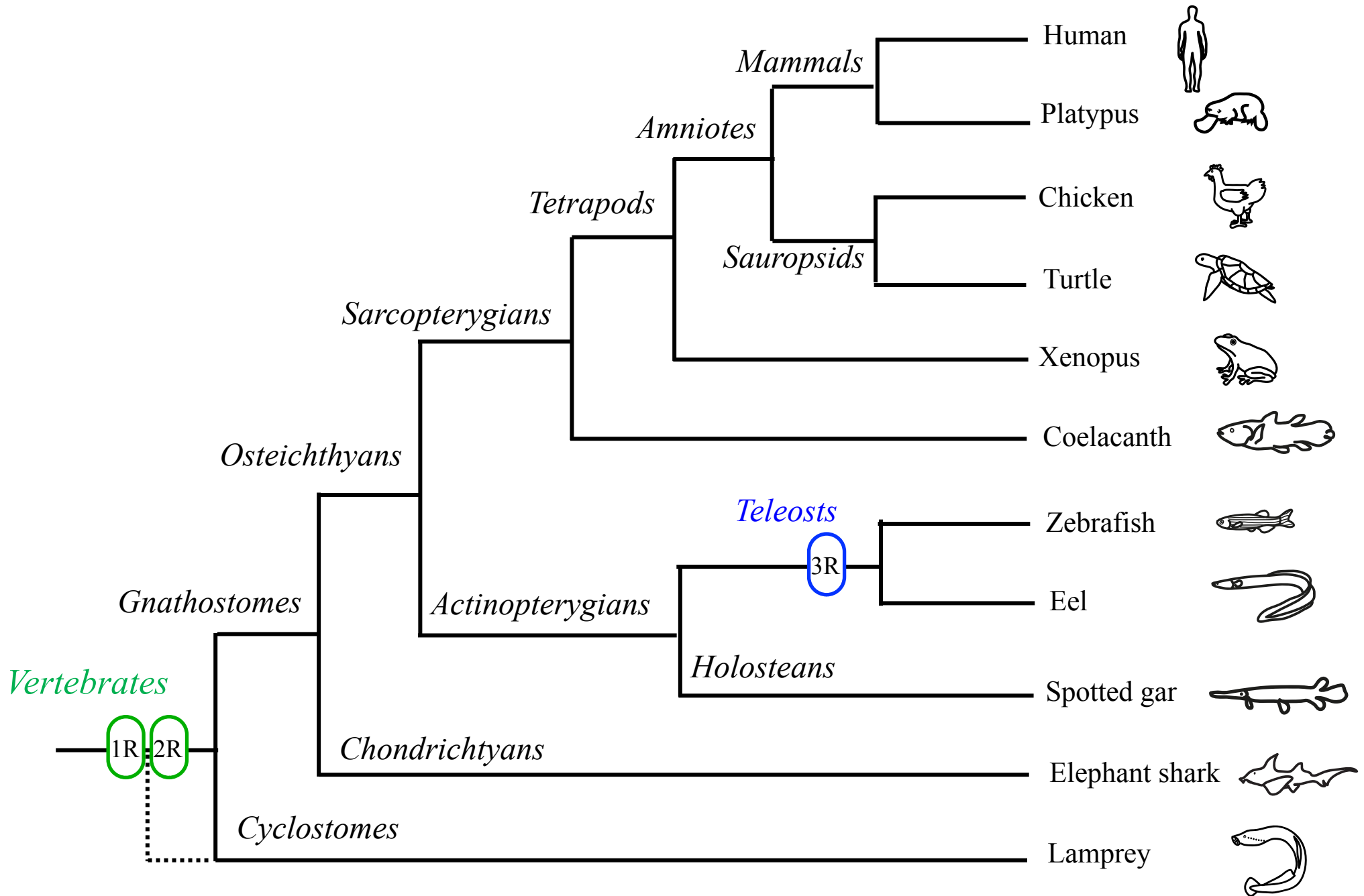
**Internal
factors**

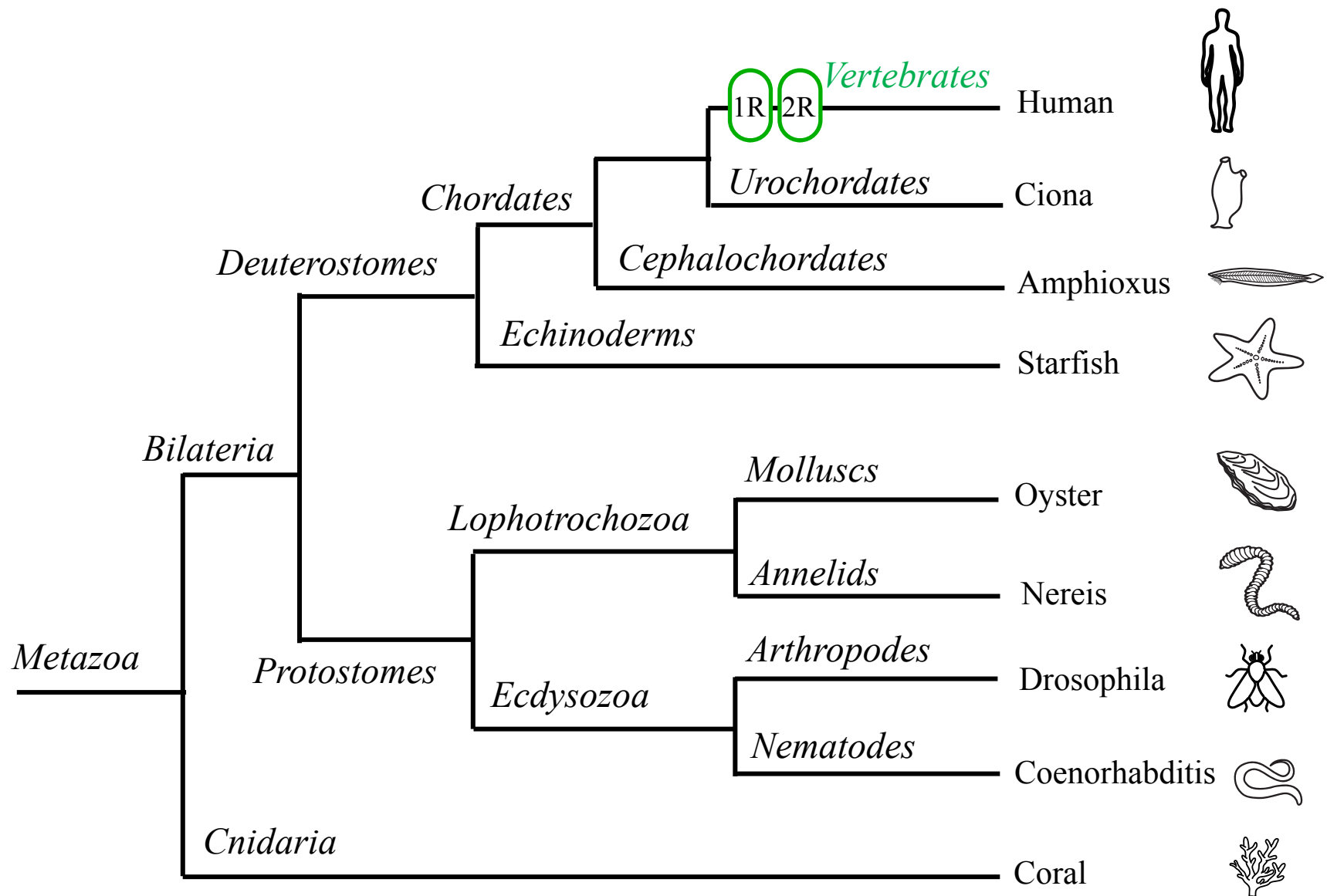
GnRH

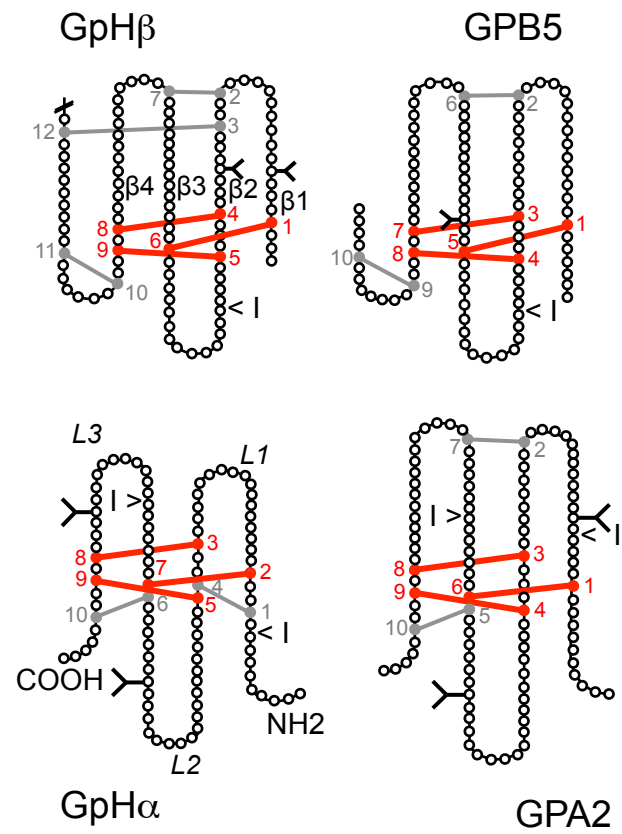
Pituitary

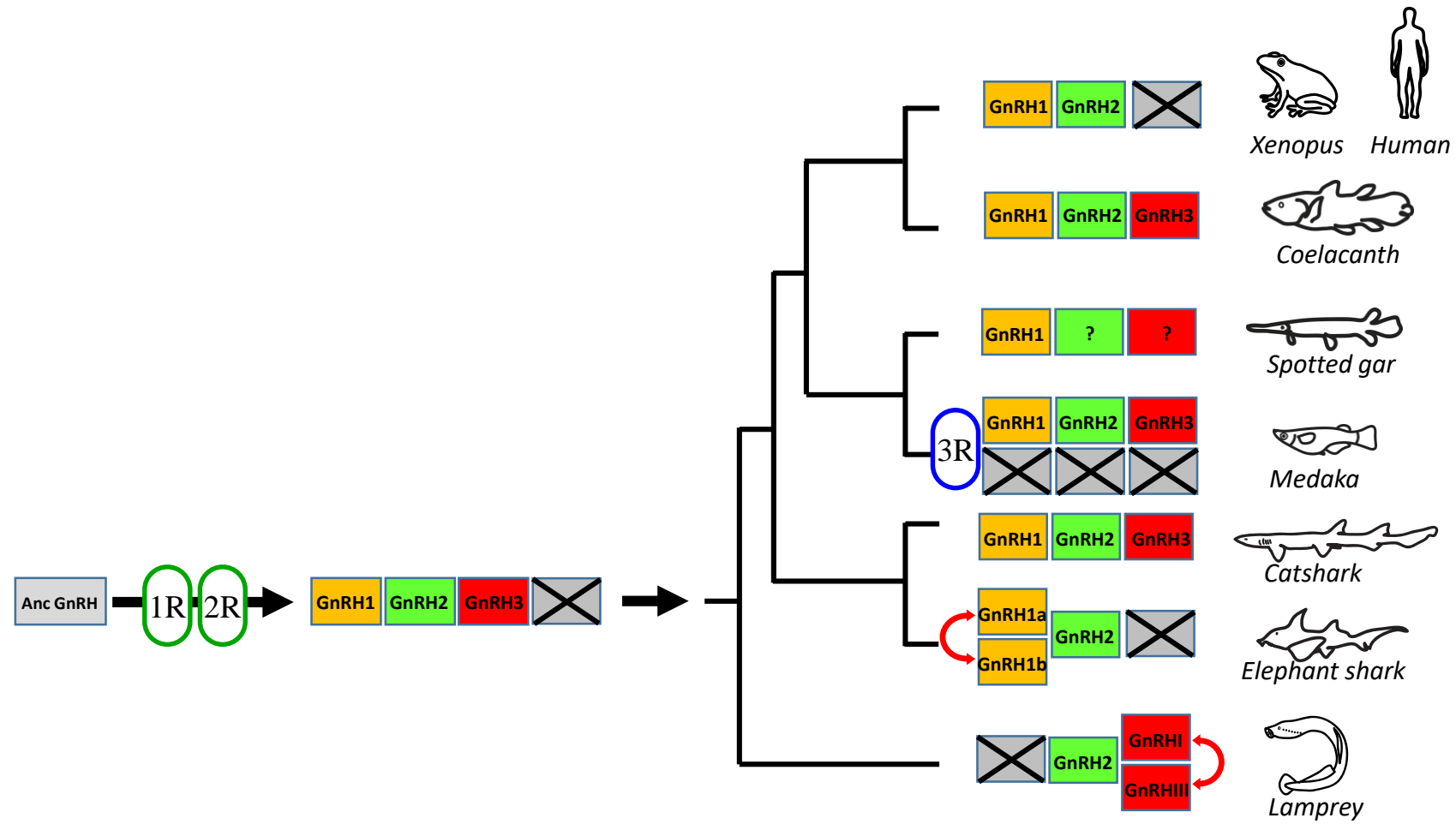
FSH LH

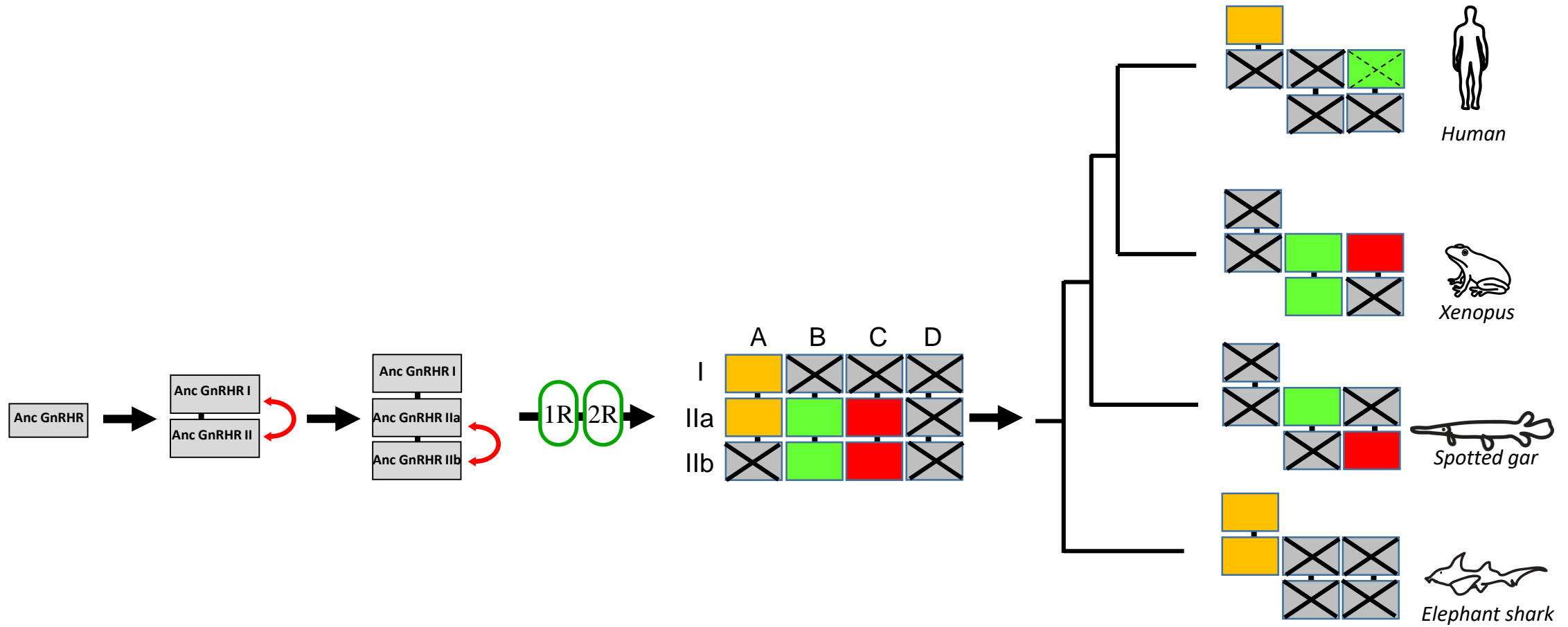
Gonads

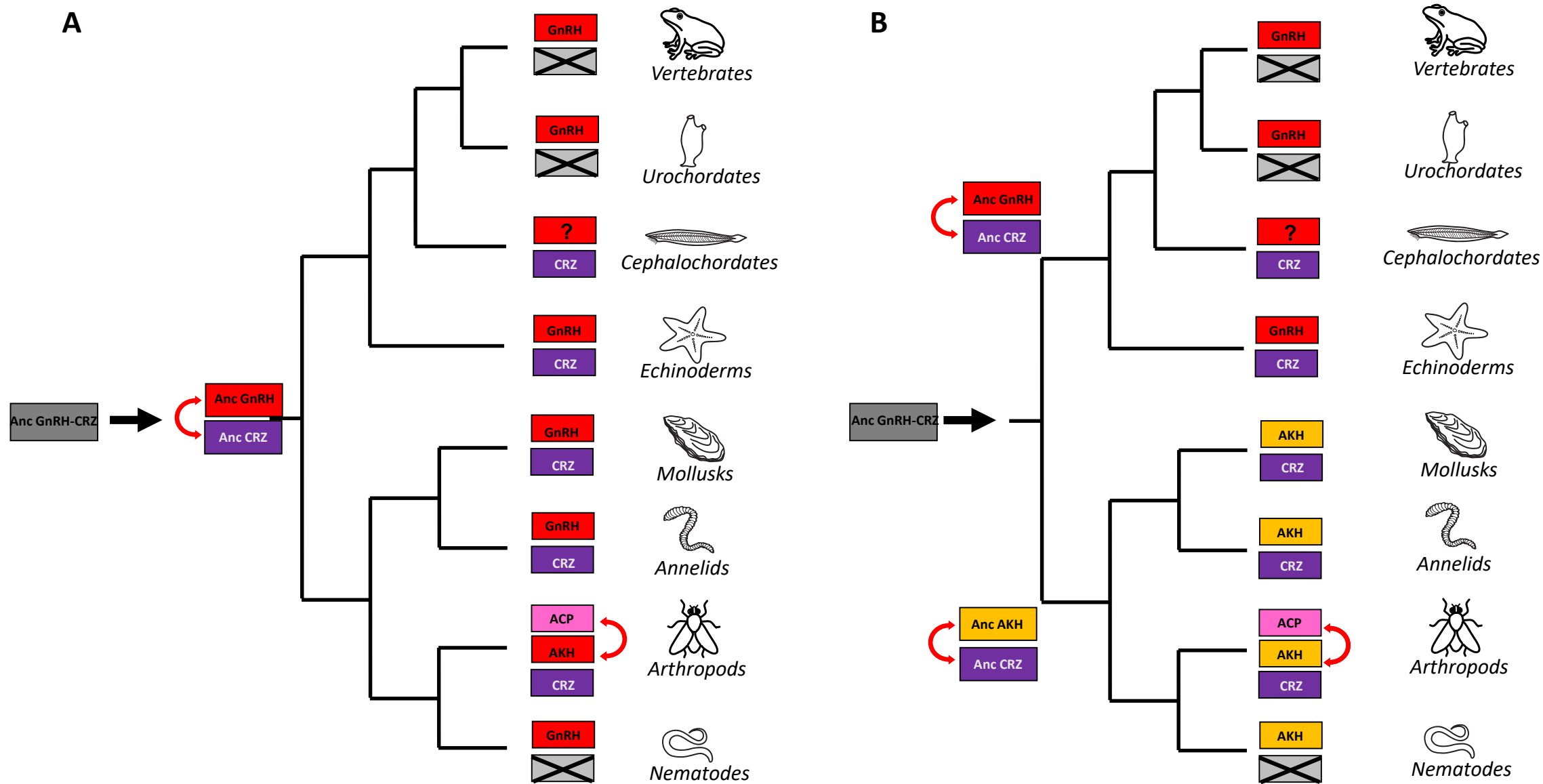






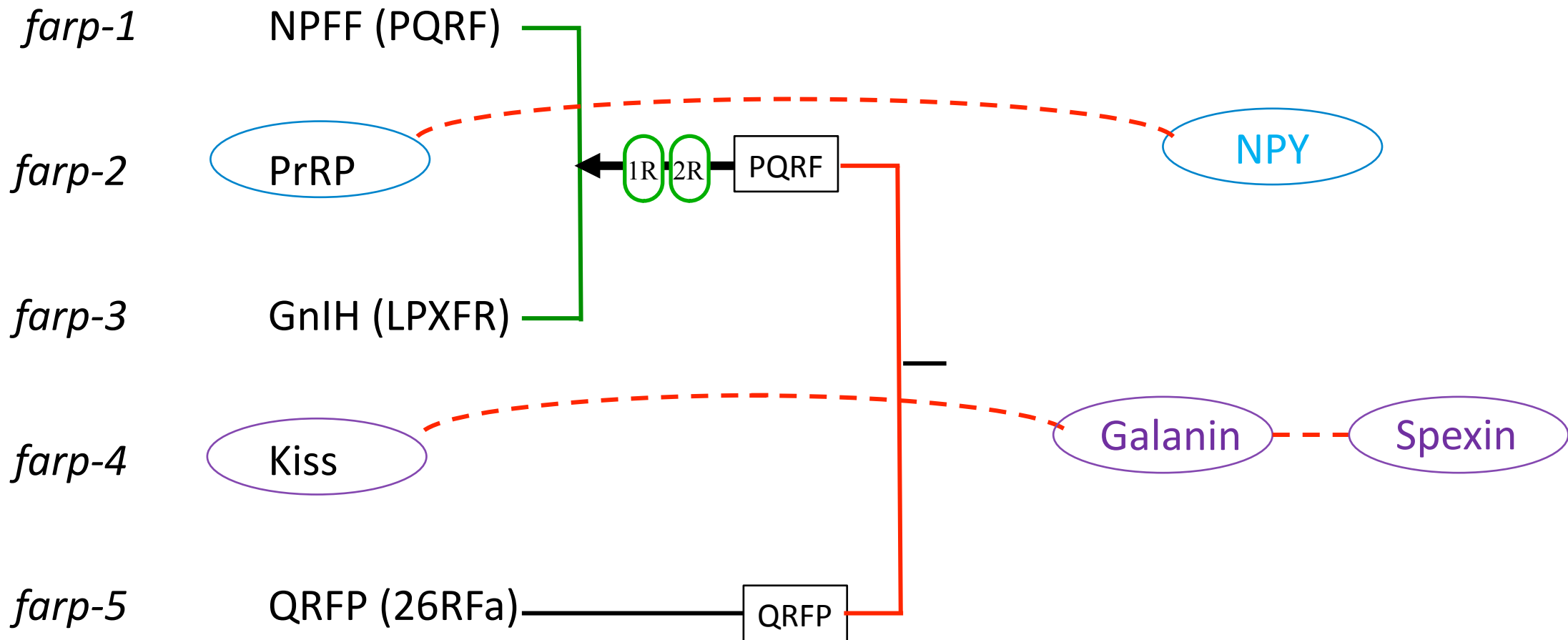


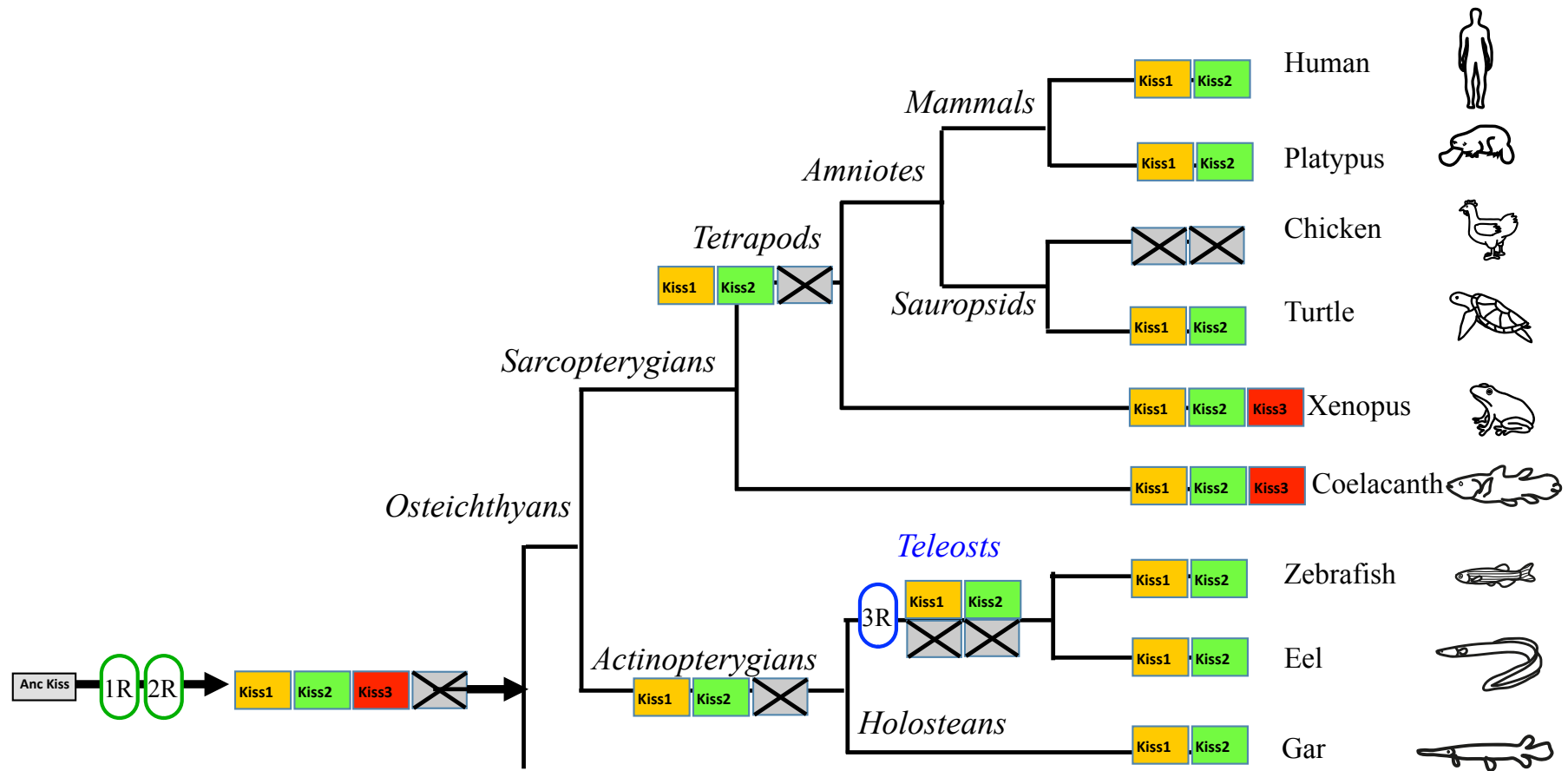


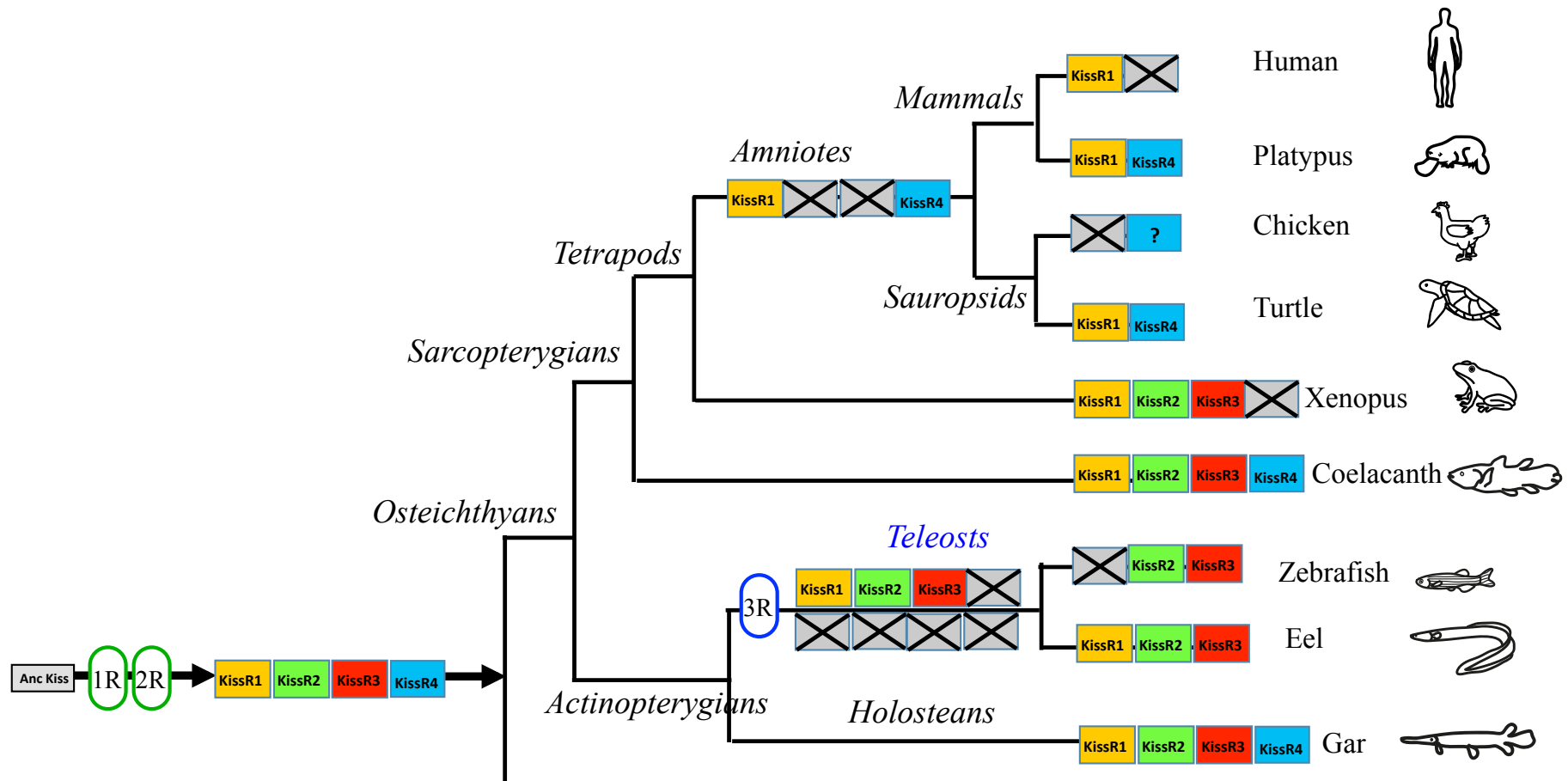


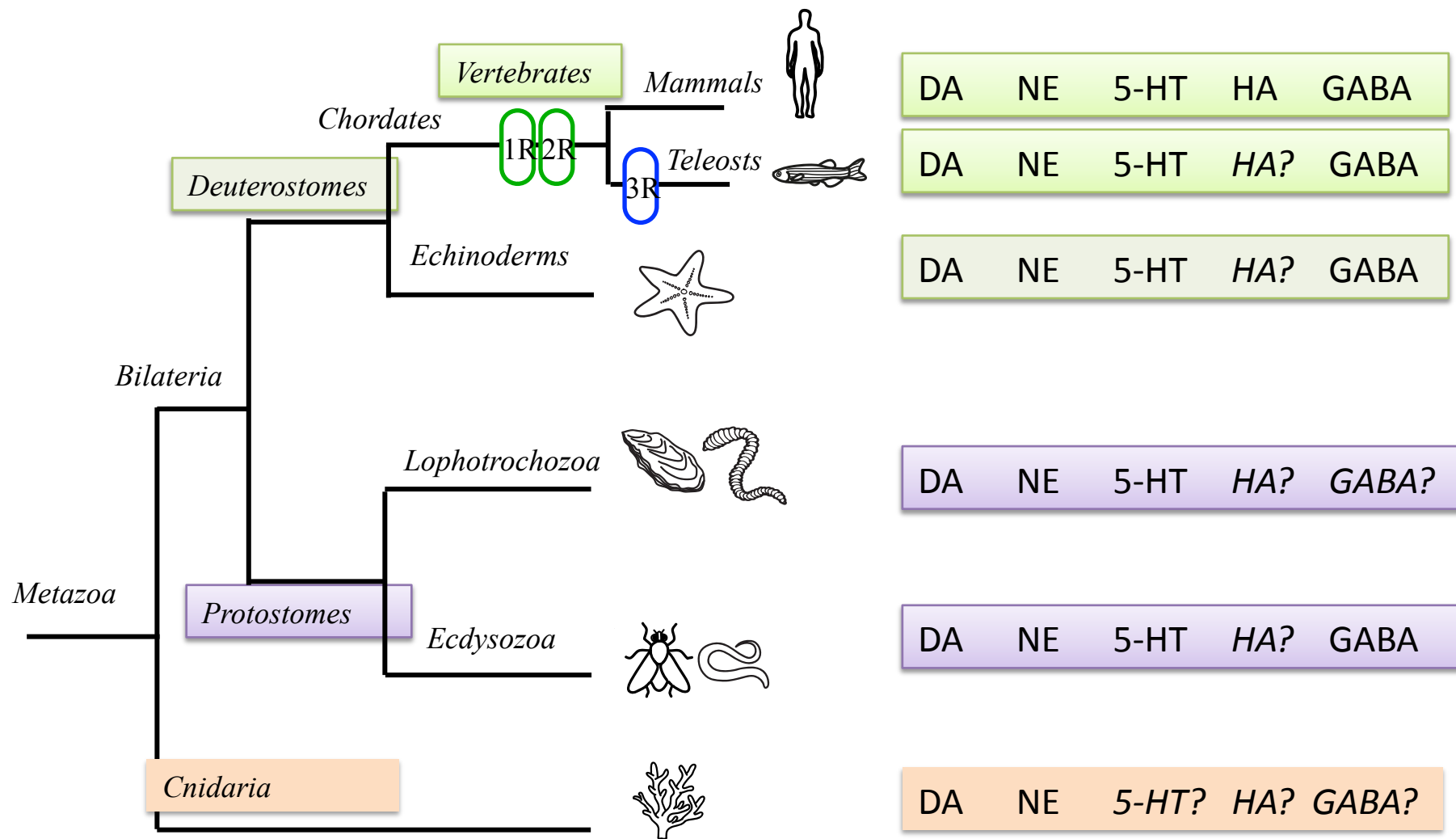
RF-amide peptide families

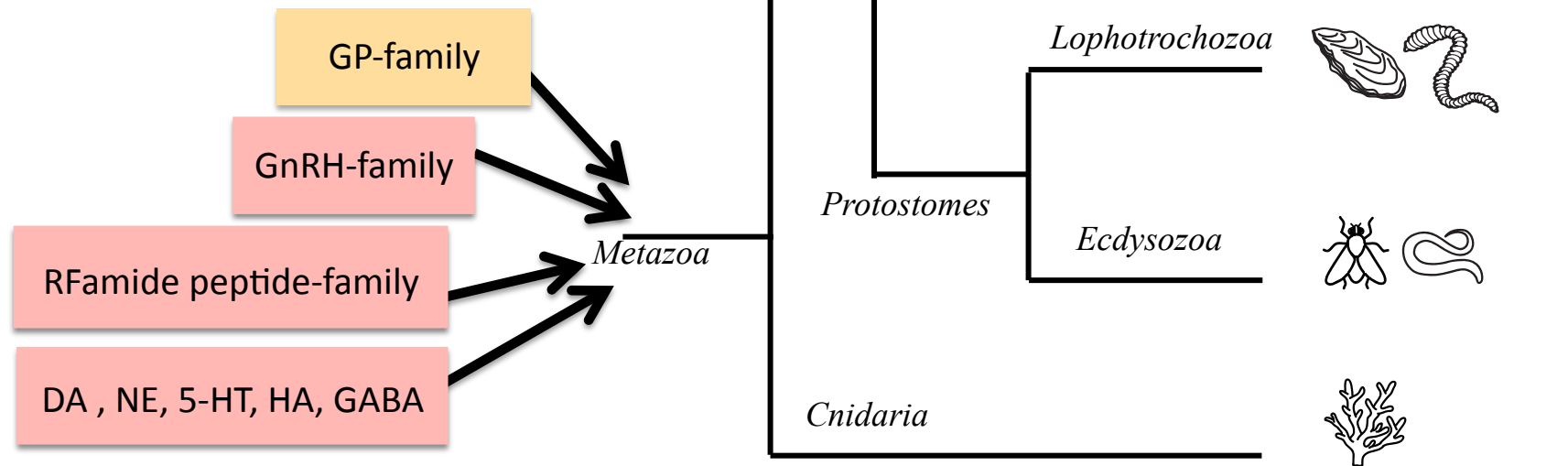
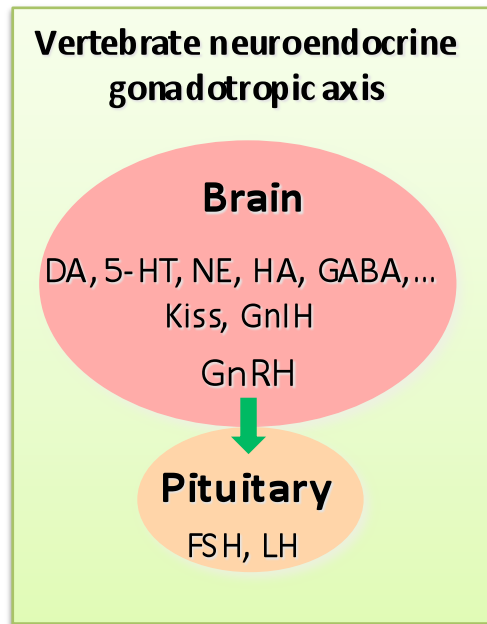
non RF-amide peptide families











	Sequences	Species	Original name	Revised name according to 905
Vertebrate GnRHs				
GnRH1	pQHWSYGLRPGa	most mammals	mGnRH	
	pQHWSYGVVRPGa	Guinea pig	gpGnRH	
	pQHWSYGLQPGa	Chicken	cGnRH-I	
	pQHWSYGLWPGa	Frog	frGnRH	
	pQHWSYGLSPGa	Sea bream	sbGnRH	
	pQHWSFGLSPGa	Medaka	mdGnRH	
	pQHWSHGLSPGa	Herring	hgGnRH	
	pQHWSHGLNPGa	Catfish	cfGnRH	
	pQHWSYGMNPGa	Whitefish	whGnRH	
GnRH2	pQHWSHGWYPGa	Chicken	cGnRH-II	
	pQHWSHGWFPGa	Lamprey	lGnRH-II	
GnRH3	pQHWSYGWLPGa	Salmon	sGnRH	
	pQHWSHGWLPGa	dogfish (catshark)	df-GnRH	
	pQHYSLEWKPGa	Lamprey	lGnRH-I	
	pQHWSHDWKPGa	Lamprey	lGnRH-III	
Tunicate GnRHs				
	pQHWSDYFKPGa	<i>Chelysoma</i>	tGnRH-1	
	pQHWSLCHAPGa	<i>Chelysoma</i>	tGnRH-2	
	pQHWSYEFMPGa	<i>Ciona</i>	tGnRH-3	
	pQHWSNQLTPGa	<i>Ciona</i>	tGnRH-4	
	pQHWSYGYMPGa	<i>Ciona</i>	tGnRH-5	
	pQHWSKGYSPGa	<i>Ciona</i>	tGnRH-6	
	pQHWSYALSPGa	<i>Ciona</i>	tGnRH-7	
	pQHWSLALSPGa	<i>Ciona</i>	tGnRH-8	
	pQHWSNKLAPGa	<i>Ciona</i>	tGnRH-9	
	pQHWSYGFSPGa	<i>Halocynthia</i>	tGnRH-10	
	pQHWSYGFLPGa	<i>Halocynthia</i>	tGnRH-11	
Cephalochordate GnRHs				
	pQILCARAFTYTHTWa	Amphioxus	AmphGnRH	CRZ
	pQEHWQYGHWYa	Amphioxus	AmphGnRH-v	?

Hemichordate CRZ

pQPHFSLKDRYRWKPa	Acorn worm	skCRZ-like
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Echinoderm GnRHs

pQVHHRFSGWRPGa	Sea urchin	SpGnRH
pQIHYNPGWGPGa	Starfish	ArGnRH

Echinoderm CRZs

HNTFSFKGRSRYFPa	Sea urchin	SpCRZ
HNTFTMGQNRWKAGa	Starfish	ArCRZ

Nematode AKH-GnRH

pQ MTFTDQWa	<i>Caenorhabditis</i>	CeAHK-GnRH
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Arthropod AKHs

pQINFSPGWGQa	Centipede	SmarAKH
pQLTFSPDWa	Fruit fly	DmAKH
pQLTFTSSWGa	Silk worm	BmAKH1
pQLNFTPWWa	Locust	LmAKH

Arthropod ACPs

pQVTFSRDWTPa	Centipede	SmarACP
pQVTFSRDWNaa	Mosquito	AgamACP
pQVTFSRDWNPa	Flour beetle	TcACP
pQITFSRSWVPQa	Prawn	MroACP

Arthropod GnRH

pQQHFRTSHFRPDNVa	Prawn	MroGnRH	?
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Arthropod CRZs

pQTFQYSGWEPa	Centipede	SmarCRZ
pQTFQYSRGWTNa	most insects	CRZ
pQTFQYSHGWTNa	Locust	LmCRZ

Mollusk AKHs

pQVSFSTNWGSa	Oyster	CgAKH	GnRH
pQIHFSPTWGSa	Owl limpet	LgAKH	GnRH
pQHFSPDWGTa	<i>Aplysia</i>	ApAKH	GnRH

Mollusk GnRHs

pQNYHFSNGWHPGa	<i>Octopus</i>	OctGnRH	CRZ
pQNYHFSNGWQPa	Oyster	CgGnRH	CRZ
pQNFHFSNGWQPa	Yessi scallop	PwGnRH	CRZ
pQNYHFSNGWYAa	<i>Aplysia</i>	ApGnRH	CRZ
pQNYHFSNGWKSa	Owl limpet	LgGnRH	CRZ

Annelid GnRHs

pQAYHFSHGWFPa	<i>Capitella</i>	CpGnRH	CRZ
pQAYHFSNGWMPa	<i>Platynereis</i>	PmGnRH-1	CRZ
pQHAHFSTGWTGFGIa	<i>Platynereis</i>	PmGnRH-2	?
pQSIHFSRSWQPa	Leech	HrGnRH	CRZ

Annelid AKHs

pQFSFSLPGKWNa	<i>Platynereis</i>	PmAKH-1	GnRH
pQLTQSLGWGSAGSSa	<i>Platynereis</i>	PmAKH-2	?

