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Gonadotrope plasticity at cellular, population and structural levels: A comparison between fishes and mammals

Romain Fontaine[a], Elia Ciani[b], Trude Marie Haug[c], Kjetil Hodne[a], Eirill Ager-Wick[a], Dianne M. Baker[d], Finn-Arne Weltzien[a,*]

[a] Department of Basic Sciences and Aquatic Medicine, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, 0454 Oslo, Norway
[b] Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, 0316 Oslo, Norway
[c] Department of Oral Biology, Faculty of Dentistry, University of Oslo, 0372 Oslo, Norway
[d] Department of Biological Sciences, University of Mary Washington, VA22401 Fredericksburg, VA, USA

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ABSTRACT

Often referred to as "the master gland", the pituitary is a key organ controlling growth, maturation, and homeostasis in vertebrates. The anterior pituitary, which contains several hormone-producing cell types, is highly plastic and thereby able to adjust the production of the hormones governing these key physiological processes according to the changing needs over the life of the animal. Hypothalamic neuroendocrine control and feedback from peripheral tissues **modulate pituitary cell activity**, adjusting levels of hormone production and release according to different functional or environmental requirements. However, in some physiological processes (e.g. growth, puberty, or metamorphosis), changes in cell activity may be not sufficient to meet the needs and a general **reorganization of cell composition** and **pituitary structure** may occur. Focusing on gonadotropes, this review examines plasticity at the cellular level, which allows precise and rapid control of hormone production and secretion, as well as plasticity at the population and structural levels, which allows more substantial changes in hormone production. Further, we compare current knowledge of the anterior pituitary plasticity in fishes and mammals in order to assess what has been conserved or not throughout evolution, and highlight important remaining questions.

1. Introduction

The pituitary is an endocrine gland found in all vertebrates. It is the key organ in the regulation of physiological processes such as growth, puberty and seasonal maturation, metabolism and homeostasis (Kelberman et al., 2009). Located below the hypothalamus, the pituitary is composed of two main parts with different developmental origins (Pogoda and Hammerschmidt, 2007): the anterior pituitary (adenohypophysis) originating from an up-growth of the mouth epithelium, and the posterior pituitary (neurohypophysis) originating from a down-growth of the diencephalon. The neurohypophysis is located posterior to the adenohypophysis in most mammals and birds. In rats (Otsuka et al., 2006) and mice (Kelberman et al., 2009), as well as in teleost fish (Norris, 2007), the neurohypophysis is located more dorsally to the adenohypophysis (Fig. 1). The neurohypophysis is mainly composed of nerve terminals from neuroendocrine cells originating in the preoptic-hypothalamic region of the brain. In contrast, the adenohypophysis contains several hormone producing cell types: gonadotropes, lactotropes, somatotropes, thyrotropes, corticotropes and melanotropes which produce, respectively, the gonadotropins (follicle-stimulating and luteinizing hormones, Fsh and Lh), prolactin (Prl), growth hormone (Gh), thyrotropin (Tsh), adrenocorticotropin (Acth) and melanocyte-

Abbreviations: ACTH, adrenocorticotropic hormone; ACTHR, adrenocorticotropic hormone receptor; BK, big/large conductance Ca^{2+} activated K^+ channel; BrdU, 5-bromo-2′-deoxyuridine; $[Ca^{2+}]_i$, intracellular calcium concentration; CRH, corticotropin-releasing hormone; ER, endoplasmic reticulum; FSH, follicle-stimulating hormone; GH, growth hormone; GHR, growth hormone receptor; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; GnRH-a, gonadotropin-releasing hormone agonist; GnRHR, gonadotropin-releasing hormone receptor; Cgα, glycoprotein α subunit; Gth, gonadotropin; Icam5, intracellular adhesion molecule-5; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; K_{Ca}, Ca^{2+} activated K^+ channel; LH, luteinizing hormone; MSH, melanocyte-stimulating hormone; MTNR, melatonin receptor; OVX, ovariectomized; PCNA, proliferating cell nuclear antigen; PRL, prolactin; PRLR, prolactin receptor; RyR, ryanodine receptors; SK, small conductance Ca^{2+} activated K^+ channel; Sl, somatolactin; SRIF, somatostatin; T3, 3,5,3′-triiodo-L-thyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TRHR, thyrotropin-releasing hormone receptor; TSH, thyrotropin or thyroid-stimulating hormone

* Corresponding author.
E-mail address: finn-arne.weltzien@nmbu.no (F.-A. Weltzien).

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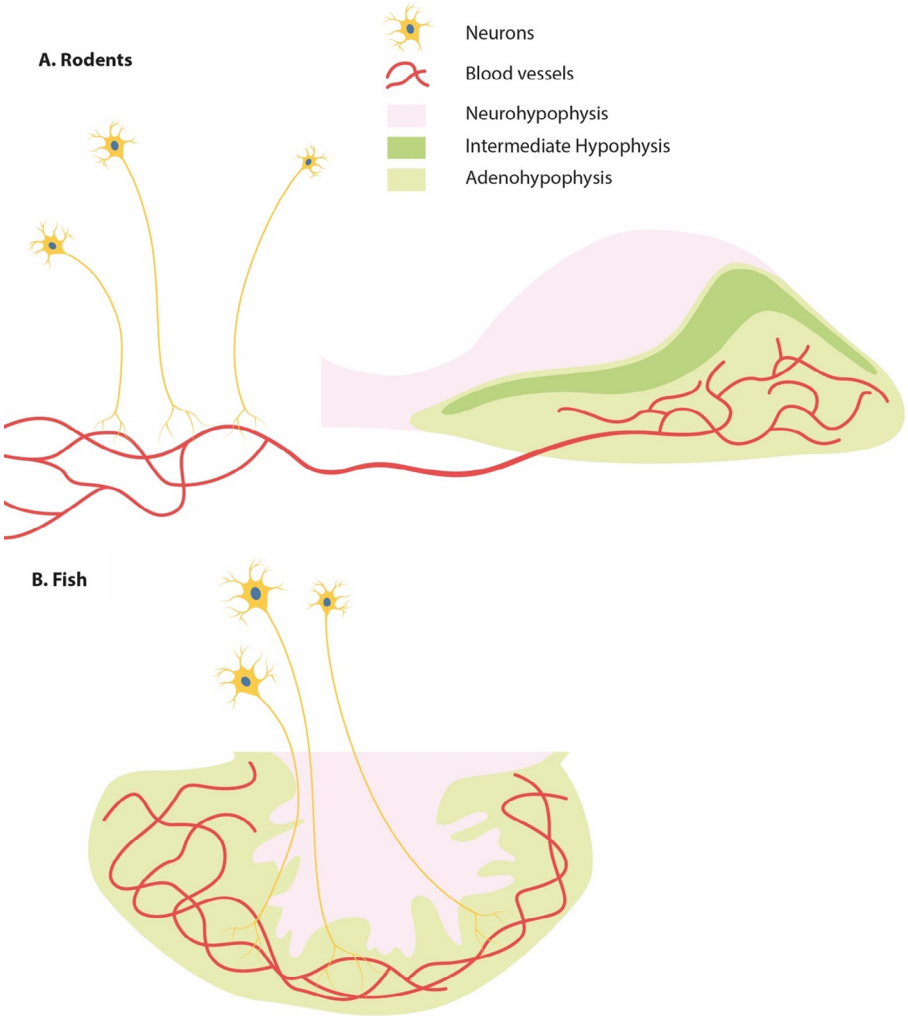

Fig. 1. Schema of the pituitary and the preoptic-hypothalamic control in rodents (A) and fish (B). The pituitary is composed of two main parts: the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis). The neurohypophysis is located posterior to the adenohypophysis in most mammals but in rodents, (rats (Otsuka et al., 2006) and mice (Kelberman et al., 2009), as well as in lower vertebrates including teleost fish (Norris, 2007), the neurohypophysis is located more dorsally to the adenohypophysis. The neurohypophysis is mainly composed of neuron terminals from neuroendocrine cells with cell soma located in the preoptic-hypothalamic region of the brain. In contrast, the adenohypophysis contains different hormones producing cell types. While preoptic-hypothalamic neurons project to the median eminence in mammals, releasing their hormones into the portal vessel system, they directly enter the pituitary and follow the blood vasculature in fish and release their neurohormones into the blood vessels or directly at the target cells.

stimulating hormone (Msh) (Zhu et al., 2007). The synthesis and secretion of these hormones are mostly controlled by factors from signaling centers in the brain which integrate internal and environmental stimuli, and from peripheral endocrine organs which provide positive and negative feedbacks.

Previously, the classical view of the pituitary was that hormone producing cells were part of fully differentiated cell populations distinguishable by their unique set of receptors, transcripts and transcriptional factors. Indeed, the prevailing model for the anterior pituitary of "one cell, one hormone" assumed that each hormone is expressed by a distinct cell type (for review (Zhu et al., 2007; Davis et al., 2016)). In mammals, this model suggests that the seven major hormones secreted by the anterior pituitary are produced by a set of six corresponding cell types, with the gonadotropins FSH and LH produced by the same cells. However, over the last 30 years, several studies have shown that some pituitary cells can also contain more than one hormone such as the gonadocorticotropes (Childs, 1991), the mammosomatotropes (Frawley and Boockfor, 1991), the somatogonadotropes (Childs, 2002), and some cells containing LH and PRL (Fukami et al., 1997). Such multihormone cells have been described in both juvenile (e.g. Seuntjens et al., 2002a; Seuntjens et al., 2002b) and adult (e.g. Villalobos et al., 2004a,b; Ho et al., 2018).

The "one cell, one hormone" model is still commonly accepted for fishes, in which even the gonadotropins are produced by two different cell types (Weltzien et al., 2014). However, pituitary cells producing more than one hormone have also been described in fishes (e.g. Hernandez et al., 2002; Golan et al., 2014; Candelma et al., 2017; Fontaine et al., 2019a). These observations lead to questions regarding the origin of these plurihormonal cells, whether they are progenitor cells in the process of differentiation toward a mono-hormonal phenotype or are differentiated cells in the process of changing phenotype (transdifferentiation).

Interestingly, the teleost pituitary differs from that of mammals in other significant ways. First, teleosts possess an additional hormone producing cell type, the somatolactotropes, which produce somatolactin (Sl), a peptidic hormone related to Prl and Gh (Kaneko, 1996; Weltzien et al., 2014). Second, two distinct populations of thyrotropes, expressing different tshb paralogues, were recently identified in Atlantic salmon (Fleming et al., 2019), likely the result of a teleost specific whole genome duplication (Maugars et al., 2014). Third, the different endocrine populations are spatially discrete through the entire lifespan in fishes (Weltzien et al., 2004; Pogoda and Hammerschmidt, 2007) whereas in mammals they are spatially discrete during embryogenesis but mosaically distributed in adults. A third difference between mammals and fish is the anatomical support for the neuroendocrine system controlling the pituitary. In mammals, preoptic-hypothalamic neurons transmit their signals to the pituitary target cells in the pituitary via a dedicated hypothalamic-pituitary portal circulatory system (Vazquez-Borrego et al., 2018) while fish appear to lack the vascular portal system and the preoptic-hypothalamic neurons send their projections in the pituitary thereby releasing their signaling molecules directly at the target cells (Fig. 1) (Weltzien et al., 2004; Zohar et al., 2010). However, recent studies in zebrafish (Golan et al., 2015) and medaka (Hodne et al., 2019) showed that preoptic-hypothalamic

neuronal projections closely follow the pituitary vasculature suggesting a possible vascular transport system in fishes.

Interestingly, several studies over the last decade have demonstrated that the pituitary microvasculature may contribute to the synchronicity of hormone secretion in mammals (Lafont et al., 2010; Hodson and Mollard, 2013; Le Tissier et al., 2018). These studies suggest that in mammals, proximity to blood vessels as well as the ability of the perivascular space to store and accumulate hormones are necessary for efficient delivery of hormones to the circulation. Analogous studies have yet to be reported for the fishes. However, new techniques such as labelling the blood vessels by cardiac injection of dyes (Fontaine and Weltzien, 2019) may help for further investigation in different species.

Finally, to adapt circulating hormone concentrations to changing needs, over an animal's life cycle, several changes in the anterior pituitary are required. All these changes that can be permanent or temporary, are grouped under the term plasticity. These include the **modulation of pituitary cell activity** through hypothalamic neuroendocrine control and highly synchronized feedback mechanisms, in addition to a general **reorganization of the anterior pituitary in terms of structure** and **cell composition**. Indeed, the two last phenomena allow larger changes in hormone production and secretion, which can be required in several physiological conditions and major developmental events (growth, puberty or metamorphosis) when changes in cellular production and release rates are not sufficient.

This review focuses on the plasticity of gonadotrope cells. It will address recent findings regarding plasticity at the cellular level for precise and fairly rapid changes in hormone production and release, and at the population and structural levels, which require more time to manifest but allows greater changes in hormone production. The mechanisms regulating these phenomena, including the roles of the main regulators of gonadotropes, gonadotropin-releasing hormone (Gnrh) and the gonadal steroids, are still not completely understood but the available knowledge will be discussed in this review in order to assess what has been conserved throughout evolution and to highlight important remaining questions.

2. Plasticity at the cellular level: regulation of hormone synthesis and secretion

In both mammals and fishes, rapid changes in levels of circulating hormones are often required. For example, in daily spawning species such as medaka, gonadotropin levels can over a few hours, increases about 12-fold around ovulation time in female medaka, to synchronize gamete maturation and spawning according to photoperiod (Ogiwara et al., 2013). Similarly, daily rhythms in gonadotropin levels are common in mammals and have been extensively characterized in rodents (reviewed by (Simonneaux and Piet, 2018)). Such rapid variations are commonly due to regulated changes in pituitary cell activity, specifically at the level of hormone synthesis and secretion. These may be considered as separate processes that can be regulated independently, the former including mRNA and protein synthesis and the latter including cell excitation and exocytosis.

Regulation of gonadotropin synthesis is mediated by the brain (with Gnrh as the main stimulator), positive and negative feedback from peripheral organs (most notably the gonads), and through paracrine signaling. Considering the complexity and diversity of the processes regulating gonadotropin synthesis, a comprehensive description of these mechanisms is outside the scope of the present review. Additionally, these mechanisms have been reviewed extensively during the last 20 years in both mammals and fish (Yaron et al., 2003; Weltzien et al., 2004; Denef, 2008; Levavi-Sivan et al., 2010; Thackray et al., 2010; Zohar et al., 2010; Stojilkovic, 2018). Therefore, in this section we will focus on the plasticity of secretion through the regulation of receptors, and cytosolic calcium dynamics.

Many molecular components are involved in gonadotropin synthesis and secretion. Therefore, modification of any one of them can lead to a change in hormone release. As with all peptide and protein hormones, gonadotropins are synthesized in the rough endoplasmic reticulum (ER), transported through the Golgi sacs and stored in secretory vesicles. Upon appropriate stimulation, the hormones are released by exocytosis into the extracellular space and diffuse into the blood circulation. In both mammals (Padmanabhan et al., 1997) and fish (Takahashi et al., 2016), gonadotrope cells have been described to display two release patterns: regulated secretion for Lh, and both regulated and constitutive secretion for Fsh. In constitutive secretion the secretory granules containing the hormones are not stored, but rather released into circulation as they are synthesized independently from signaling. In contrast, in regulated secretion, the secretory granules are released in bursts upon activation of specific receptors, allowing the cell to secrete large amounts of hormone over a short period of time. Note that although constitutive secretion may not be regulated, the hormone production (transcription and translation) may be, as is the case for Fsh.

2.1. Regulation of sensitivity to ligands

Because the hormones and neurotransmitters regulating the pituitary act via specific receptors, the density of such receptors in a target cell is an essential factor in the response. Indeed, the sensitivity to ligands is a key factor determining pituitary cell activity and varies according to the number of receptors among other factors.

Variations in receptor density in pituitary cells have been described for several regulatory signals. For example, mRNA levels of melatonin receptors (Falcon et al., 2007; Falcón et al., 2010; Falcón et al., 2011) and kisspeptin receptors (Ando et al., 2018) vary across the seasons, the different life stages, or physiological stages of an animal. In this review, we focus on variation in gonadotropin-releasing hormone receptor (Gnrhr) levels on gonadotrope cells, as an example of how gonadotrope cellular activity may be regulated by variations in receptor expression. The sensitivity of the pituitary gland to Gnrh varies greatly both among and within species, with response depending not only on sex, age, and season but also time of day. Indeed, the expression of specific Gnrhr isoforms has been shown to change throughout the life cycle of the animal modulating the pituitary sensitivity to Gnrh, as discussed below.

In mammals, the effects of GnRH are mediated via one or two receptor isoforms (Hapgood et al., 2005). On the other hand, it is characteristic of teleost species to express multiple receptor paralogs (Hildahl et al., 2011; Sefideh et al., 2014; Williams et al., 2014) resulting from the teleost-specific 3rd (3R, common to all teleosts) and 4th (4R, specific to salmonids) whole genome duplications (Allendorf and Thorgaard, 1984; Jatllon et al., 2004; Berthelot et al., 2014). For instance, some species have retained five (European seabass; (Moncaut, 2005); masu salmon, *Oncorhynchus masou;* (Jodo et al., 2003)) or six (Atlantic salmon, *Salmo salar*; (Ciani et al., 2019)) *gnrhr* paralogs. Teleosts are therefore interesting models to study gonadotrope plasticity from an evolutionary perspective, considering that the different paralogs may have assumed specific roles in the Gnrh mediated pituitary response. Phylogenetic analyses of teleost Gnrhr sort the receptors in two clusters, type 1 and 2 (Hildahl et al., 2011; Sefideh et al., 2014; Ciani et al., 2019). Although information regarding the functional role of the different receptor types in teleosts is limited, several studies have implicated type 2 receptors in the control of gonadotropin synthesis and release (Hildahl et al., 2011; Melo et al., 2015; Lumayno et al., 2017; von Krogh et al., 2017; Ciani et al., 2019; Hodne et al., 2019). A common characteristic of all these studies is the variation in receptor expression throughout the year, peaking during critical periods of the reproductive cycle.

2.1.1. Variation during sexual maturation

2.1.1.1. Mammals. Among mammals, the variation of Gnrhr expression and the differential response of the pituitary to GnRH stimuli in different phases of the reproductive cycle has been studied most

extensively in rats (reviewed by (Janjic et al., 2017)). In females, pituitary *Gnrhr* expression increases during the first two week of development, declines afterwards and remains low until adult stage, where it peaks again at 7–8 weeks of age. In males, the expression profile is slightly different, peaking at the end of the juvenile period at 5 weeks of age (Wilson and Handa, 1997; Bjelobaba et al., 2015). The peak of *Gnrhr* expression correlates well with expression of all gonadotropin subunit genes in both sexes (Bjelobaba et al., 2015). In addition, *Gnrhr* peaks in the morning during diestrus I and II and proestrus phase in female rats and declines after the LH surge (Kakar et al., 1994; Schirman-Hildesheim et al., 2005; Schirman-Hildesheim et al., 2006). Similarly, in sheep, both GnRHR mRNA and protein increase during the luteal phase and declines after the preovulatory LH surge (Brooks et al., 1993; Padmanabhan et al., 1995; Ciechanowska et al., 2010).

2.1.1.2. Fish. Teleost *gnrhr* paralogs are named in the present review according to the phylogeny proposed in (Ciani et al., 2019). For clarity, original names from publication are also given in parenthesis when different. Numerous studies in teleosts have found that one or several *gnrhr* mRNA paralogs increase sharply during critical reproductive periods, often coincident with increased *gnrh* and gonadotropin expression. In chub mackerel (*Scomber japonicas*), pituitary expression of *gnrhr2ba1* (named *gnrhr1* by the authors) increases in both sexes during sexual maturation, concomitant with increased *gnrh1* and *lhb* (Lumayno et al., 2017). In female Atlantic cod, the expression of three receptor paralogs, *gnrhr1cb*, *gnrhr2ba1* and *gnrhr2ba2*, (*gnrhr1b*, *gnrhr2a* and *gnrhr2c*) was detected in the pituitary gland (Hildahl et al., 2011). Among them, *gnrhr2ba1* was differentially expressed during the reproductive cycle, increasing during sexual maturation. Subsequently, the expression of this paralog was localized in both *lhb*- and *fshb*-expressing cells via single-cell qPCR (von Krogh et al., 2017). In Atlantic salmon, the expression of five *gnrhr* paralogs was detected in the pituitary gland of male parr during sexual maturation (Ciani et al., 2019). Of those, *gnrhr2bbα* showed differential expression with regards to maturational stage and gonadotropin expression in both maturing parr (Ciani et al., 2019) and post smolt (Melo et al., 2014; Melo et al., 2015). Interestingly, the expression of this gene was detected specifically in *lhb*-expressing cells and not in *fshb*-expressing cells via *in situ* hybridization (Ciani et al., 2019). Five *gnrhr* paralogs were also detected in masu salmon pituitary gland, with seasonal variation in their expression levels with some differences between sexes (Jodo et al., 2005). In European eel, pituitary expression of *gnrhr1ca* in female and *gnrhr2bb* in both sexes (*gnrhr1a* and *gnrhr2*), increased in parallel with gonad development during hormonally induced sexual maturation (Peñaranda et al., 2013). In pejerrey (*Odontesthes bonariensis*), pituitary *gnrhr2a* expression increased during gonadal maturation coincident with increased brain *gnrh3* expression (Guilgur et al., 2009). In female European sea bass (*Dicentrarchus labrax* (González-Martínez et al., 2004)), *gnrhr2ba1* (dl-GnRHR-2A), detected in all *lhb*-expressing cells and in some *fshb*-expressing cells via *in situ* hybridization, increased during late vitellogenesis, and decreased during maturation, spawning and post-spawning. The described variations in expression levels could be due to some combination of a gene expression *per se*, a cellular proliferation, or a phenotypic conversion. However, because of the techniques used (based on whole pituitary analysis), it is not possible to discriminate among their relative contributions. Therefore, further studies are needed to investigate the regulation of gnrhr as well as its role in gonadotrope activity throughout maturation.

2.1.2. Daily variation

The expression of *gnrhr* varies not only over long periods of time, but also throughout the day according to daily physiological rhythms. In this case, the contribution of cellular proliferation and phenotypic conversion may be considered limited or absent. These daily and circadian fluctuations have been reported in both mammalian and teleost species.

2.1.2.1. Mammals. In ovariectomized (OVX) and intact female rats, hypothalamic and pituitary mRNA levels of both *Gnrh* and *Gnrhr* display daily variation over the four days of the estrous cycle (Schirman-Hildesheim et al., 2006). Pituitary *Gnrhr* increases in the morning and evening with slight variation in timing between intact and OVX rats and the different days of the cycle, showing however a good correlation with pituitary and hypothalamic *Gnrh* mRNA levels (Schirman-Hildesheim et al., 2005; Schirman-Hildesheim et al., 2006).

2.1.2.2. Fish. In fish, Paredes et al. (2019) reported synchronized, daily rhythms of gene expression at all levels of the brain-pituitary-gonad and brain-pituitary-liver axes in zebrafish (*Danio rerio*). At the pituitary level, *gnrhr2ba* (*gnrhr2*) peaks at the beginning of the light phase in both sexes, before increases of both *lhb* and *fshb*. The increase in receptor expression may intensify the responsivity of the pituitary gland to Gnrh stimulation resulting in increased gonadotropin expression. Interestingly, daily variation in expression of a second receptor paralog, *gnrhr1cb* (*gnrhr3*), was seen only in males, and peaked at the beginning of the dark phase, suggesting different functions for the two receptor isoforms. Daily fluctuations in *gnrhr* expression have been detected also in Atlantic salmon pituitary (Ciani et al., 2019). Two of the paralogs (*gnrhr2bbα* and *gnrhr2bbβ*) derived from the salmonid-specific whole genome duplication show season-dependent daily fluctuations. Both receptors peak in the morning and decline at night during spring, when the fish are sexually maturing. However, in autumn when the fish were still immature, there was no significant changes in *gnrhr2bbα* and *gnrhr2bbβ* during a 24 h cycle (Fig. 2). While *gnrhr2bbα* has been localized exclusively in *lhb*-expressing cells and thus seems tightly linked to *lhb* regulation, the cellular localization and the functional role of *gnrhr2bbβ* are still unknown.

2.1.3. Variation in response to social interactions

In vertebrates, the pituitary gland responds to social stimuli by adjusting hormonal production therefore influencing the reproductive capability and other physiological parameters. Evidence of this plasticity have been reported in both mammals and fish.

2.1.3.1. Mammals. Similar to the effects of social interactions on the stress endocrine axis, for instance influencing the secretion of adrenocorticotropic hormone (e.g. Hennessy, 1997; Levine, 2001; Keeney et al., 2006; Shafia et al., 2017), several studies have reported the influence of social interactions on the gonadotrope axis. Indeed, effects of parental care on the offspring reproductive behavior were reported in rats (Cameron et al., 2008). Maternal grooming behavior during the first week post-partum increases plasma LH levels at proestrus and increases the positive feedback of estradiol on plasma LH of female offspring. However, whether these effects are mediated by changes in Gnrhr is not known, and remains to be investigated.

2.1.3.2. Fish. Although studies on the influence of social status and behavior on pituitary plasticity are limited, studies in the African cichlid fish, *Astatotilapia burtoni,* suggest they indeed play a role (reviewed by (Maruska and Fernald, 2013)). In this species, hierarchies form among males, and only a small number of dominant individuals have access to spawning grounds and mature females. Interestingly, the dominant/subordinate status is reversible, and the same individual may switch several times over its lifespan. Stable dominant males express higher gonadotropin and *gnrhr* expression levels, compared to stable subordinate males (Au et al., 2006; Maruska et al., 2011). During the transition from subordinate to dominant status, the pituitary gland quickly responds to increased Gnrh1 neuronal activity by modulating the expression and release of several hormones. Both Fsh and Lh mRNA and plasma protein levels

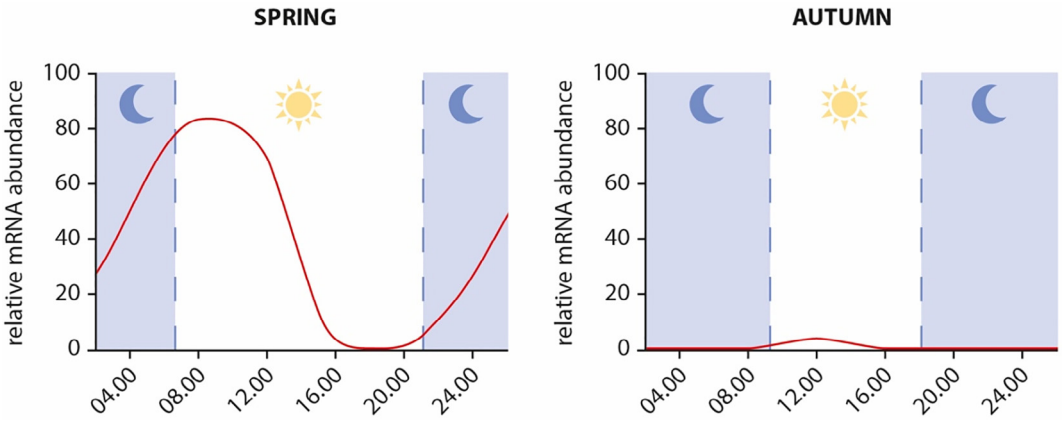

Fig. 2. Schematic representation of mRNA transcript levels of a particular gnrhr paralog (*gnrhr2bb)* in Atlantic salmon over 24-hours, in spring when the fish undergo sexual maturation, and in autumn (modified from Ciani et al. (2019)). *gnrhr* expression presents an important season dependent daily rhythm, suggesting that cell sensitivity to the ligand may change over the 24-hour cycle, thus leading to differential hormonal synthesis and secretion by the targeted pituitary cells.

(Maruska et al., 2011), together with estrogen receptor and aromatase mRNA (Maruska and Fernald, 2013), are upregulated 30 min after the rise in rank. Pituitary *gnrhr* (GnRH-R1) mRNA also increase after the rise in status, reaching levels comparable to stable dominant males at 120 h (Maruska et al., 2011). The rapid induction in gonadotropin synthesis and release shows that the pituitary rapidly changes its sensitivity following elevation in the hierarchy of competitive males, allowing them to quickly become reproductively active.

2.1.4. Hormonal regulators of Gnrhr expression

The changes in receptor levels described above are likely due to a complex interplay of endocrine and neurohormonal signals. Among the myriad signals, the most intensely studied are the ligands themselves and sex steroid feedback.

2.1.4.1. Mammals. In mammals, both positive and negative effects of GnRH on GnRHR expression have been reported, depending on the species and the physiological state of the animal. Indeed, GnRH has been found to upregulate *Gnrhr* transcription *in vivo* in ewe (Turzillo et al., 1995; Clarke et al., 2005) and cow (Vizcarra et al., 1997), and *in vitro* in rats (Cheon et al., 1999; Cheon et al., 2000; Bjelobaba et al., 2016). In contrast, prolonged exposure to GnRH *in vivo* downregulates *Gnrhr* in ewe (Turzillo et al., 1998), and both *in vivo* (Han et al., 1999) and *in vitro* (McArdle et al., 1987; McArdle et al., 1995) in rats, demonstrating that the duration of the exposure is in fact a critical factor. For instance, in pituitary cell cultures from 7 week old female rats, GnRH induces *Gnrhr* expression with a peak of expression at 6 h (Bjelobaba et al., 2016). Longer GnRH exposure does not further increase *Gnrhr* expression (Bjelobaba et al., 2016). Therefore pulsatile GnRH release, typical in mammals, is necessary not only for gonadotropin synthesis and release, but also for appropriate *Gnrhr* expression (Kaiser et al., 1997; Ferris and Shupnik, 2006).

Sex steroids also regulate Gnrhr in mammals. Estradiol upregulates both Gnrhr mRNA and GnRHR protein *in vivo* in cow (Vizcarra et al., 1997) and sheep (Adams et al., 1996) pituitary, as well as in ovine pituitary cell cultures (Gregg et al., 1990; Laws et al., 1990; Sealfon et al., 1990). Conversely, progesterone generally inhibits Gnrhr transcription in mammals, e.g. it downregulates pituitary *Gnrhr in vitro* in ovine (Turzillo and Nett, 1999), and rat both *in vitro* (McArdle et al., 1995; McArdle et al., 2009) and *in vivo* (Bauer-Dantoin et al., 1995). Interestingly, binding studies showed that testosterone and Gnrhr in male rats are inversely correlated *in vivo* (Chan et al., 1981; Dalkin et al., 1981), suggesting that testosterone might exert direct or indirect negative feedbacks on pituitary Gnrhr during sexual maturation in male rats.

2.1.4.2. Fish. In teleosts, Gnrh also affects levels of its own receptors, and as in mammals, the effects vary according to species and physiological status. For instance, Gnrh stimulated *gnrhr2ba1* (GnRH-R) mRNA levels in pituitary primary cell culture from maturing males hybrid tilapia (Levavi-Sivan et al., 2004). Conversely, Gnrh exposure strongly inhibited *gnrhr2bbβ* (*gnrhr1*) expression in pituitary cell cultures from immature males coho salmon (Luckenbach et al., 2010). Gnrh also modulates the number of Gnrhr present in cells, thus controlling pituitary sensitivity in teleosts. In binding studies on pituitary sections from goldfish, treatment with Gnrh significantly reduced pituitary Gnrhr content, thus leading to desensitization (Habibi, 1991). *In vivo* effects of Gnrh analogs (Gnrh-a) have also been used to investigate Gnrhr regulation in teleosts. In masu salmon, implanted Gnrh-a increase expression of all *gnrhr* paralogs, with efficacies varying between sexes and with time of the year (Jodo et al., 2005). In addition, the response to Gnrh-a has been shown to be dose dependent in hybrid tilapia. Gnrh-a injections induce *gnrhr2ba1* (GnRH-R) expression at low doses but inhibits at high doses (Levavi-Sivan et al., 2004). Interestingly, pulsatility of Gnrh release similar to that observed in mammals has not been found in fish so far. Since constant GnRH treatment does not inhibit gonadotropes in fish like it does in mammals, pulsatility may not be essential for gonadotrope function. However, the different responses to constant GnRH described above could be due to species differences or differences in physiological stage. Thus, whether Gnrh pulsatility exists or not in fish, and the role it may play in the regulation of Gnrhr remain open questions.

As in mammals, sex steroids affect *gnrhr* expression, but in a paralog-specific manner. In Atlantic cod, estradiol and testosterone increased *gnrhr2ba1* but not *gnrhr1cb (gnrhr2a; gnrhr1b)* expression *in vitro* in pituitary cells collected from mature and post-spawning fish, whereas dihydrotestosterone increased *gnrhr2ba1* in cells from maturing fish (von Krogh et al., 2017). In Atlantic salmon, *gnrhr2bba* expression increased with testosterone injections (Melo et al., 2015). In the black porgy (*Acanthopagrus schlegeli*), estradiol and testosterone increased *gnrhr2ba1* (*gnrhr1*), but not *gnrhr2bb* (*gnrhr2*), expression both *in vivo* and *in vitro*, while 11-ketotestosterone inhibited *gnrhr1* expression *in vivo* (Lin et al., 2010). In Nile tilapia, estradiol upregulates *gnrhr2ba2* (*gnrhr3*) expression both *in vivo* and *in vitro* (Levavi-Sivan et al., 2006).

Most studies to elucidate the roles of the different pituitary gnrhr isoforms in fish have focused on gene expression analysis. Information regarding the receptor protein abundance, localization and function is still very limited. Gene expression analysis alone provides useful but incomplete information on pituitary sensitivity to ligands. Future research should aim to fill the gaps regarding the changes and regulation of protein levels, localization and activity.

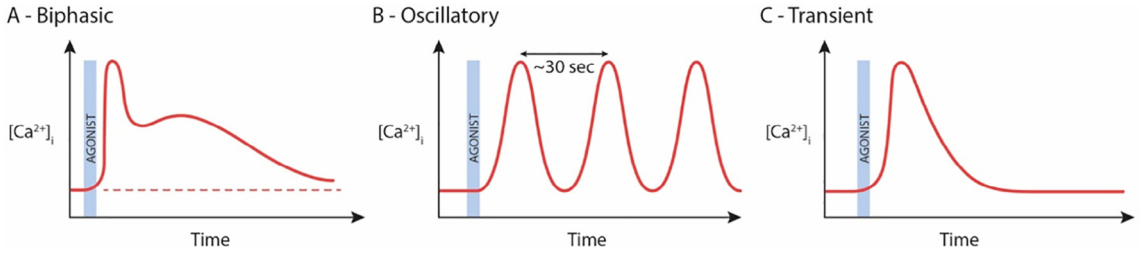

Fig. 3. Illustrative representation of different agonist-induced cytosolic Ca^{2+} responses observed in pituitary endocrine cells. The blue rectangle represents timing of agonist stimulus. A) Biphasic calcium responses in which the cell usually acquires Ca^{2+} from two sources: a release of calcium from internal stores observed as an initial peak, followed by a second delayed response observed as a longer lasting plateau -when influx of Ca^{2+} from the extracellular space occurs. Typical biphasic Ca^{2+} response last for 3 or more minutes. Often one can observe that the $[Ca^{2+}]_i$ does not return to baseline. B) Oscillatory Ca^{2+} responses are due to alternating IP3 induced Ca^{2+} release and relatively quick reuptake before new release. These oscillations are independent of extracellular Ca^{2+}. However, the extracellular Ca^{2+} influx is necessary for replenishing intracellular Ca^{2+} stores and to maintain the oscillations. C) Transient Ca^{2+} responses are transient increases in $[Ca^{2+}]_i$. The response returns to baseline values within 1–2 min. The Ca^{2+} could potentially come from both internal and external sources.

2.2. Regulation of intracellular calcium signaling

All gonadotrope cells, whether they exhibit the constitutive or the regulated release pattern, utilize the same mechanisms to mediate release as all other exocytotic cells (Park and Loh, 2008; Thorn et al., 2016). The common primary regulator of release is the intracellular Ca^{2+} level $[Ca^{2+}]_i$ (Neher and Zucker, 1993; Rupnik et al., 2000). Ca^{2+} is required for vesicle fusion (see review (Südhof and Rothman, 2009)) and a tight regulation of $[Ca^{2+}]_i$ is critical for appropriate pituitary cell activity. Endocrine cells rely on two sources of Ca^{2+}: intracellular stores and extracellular space. Both Ca^{2+} sources are usually recruited during agonist stimulation, however their relative contribution to hormone secretion differs.

2.2.1. Mammals

The biophysical properties and Ca^{2+} dynamics regulating hormone secretion in pituitary cells have been extensively studied in mammals (See review by (Stojilkovic et al., 2010)). In gonadotrope cells as in other pituitary endocrine cells, Ca^{2+} is released from internal stores in response to G-protein and subsequent generation of inositol 1,4,5-trisphosphate (IP3). IP3, in turn, binds IP3 sensitive receptors (IP3R), a type of calcium channel situated on the ER membrane (Guillemette et al., 1987) found in all pituitary endocrine cells (Stojilkovic et al., 1990; Stojilković et al., 1991; Ashworth and Hinkle, 1996; Zingg, 1996; Suárez et al., 2002). Activation of IP3R generates an extracellular-independent elevation of $[Ca^{2+}]_i$. The elevation in $[Ca^{2+}]_i$ following IP3R activation and the subsequent cellular responses vary among cells, and this is reflected by the cellular micro domains where the IP3R operate (Stojilkovic et al., 2005b). Moreover, the presence of the different variants and isoforms of IP3R which have different properties also contributes in differential responses of the cells (Berridge, 1993). As explained further below, feedback mechanisms greatly affect the Ca^{2+} dynamics.

In addition to IP3R, ryanodine receptors (RyR), which are also Ca^{2+} channels on the ER membrane but activated by elevated $[Ca^{2+}]_i$, may also play a role. RyR were detected in female rat pituitary. Blocking these channels decreased the rhythmic release of LH following GnRH stimulation suggesting their presence in gonadotrope cells (Sundaresan et al., 1997). However, recent single-cell transcriptome profiling of mice pituitaries questions the overall presence of RyR in the pituitary (Cheung et al., 2018) making unclear how important RyR are in controlling pituitary hormone release. Nevertheless, caution should be made as single-cell transcriptome profiling is less sensitive compared to PCR, and sex or species differences may also exist. Therefore, further functional studies are required to determine if RyR play a direct role $[Ca^{2+}]_i$ regulation and in pituitary hormone secretion.

As mentioned, the cellular responses to IP3R activation are diverse, but also may depend on the model organism and the type of preparations used. $[Ca^{2+}]_i$ measurements in gonadotropes using rat and mice primary dispersed cells where paracrine input is removed display biphasic and oscillatory extracellular-independent Ca^{2+} fluctuation when exposed to GnRH (Stojilkovic and Catt, 1992), similar to that seen in mice corticotropes after CRH stimulation (Tse and Frederick, 1998). However, not all mammalian gonadotropes exhibit $[Ca^{2+}]_i$ oscillations in response to GnRH. Electrophysiological recordings from ovine gonadotropes revealed a biphasic change in the membrane potential after GnRH stimulation (Heyward et al., 1995), likely reflecting changes in $[Ca^{2+}]_i$. Biphasic $[Ca^{2+}]_i$ and membrane voltage responses to specific agonists are also observed in several different immortalized gonadotrope cell lines derived from mouse and rat pituitary (Anderson et al., 1992; Thomas et al., 1996; Zemkova et al., 2013).

Compared to dissociated cell cultures, the agonist-induced $[Ca^{2+}]_i$ responses are more complex in pituitary slices, in which the three-dimensional cellular environment is more intact. Thus, by preserving the local environment, an increased heterogeneity among the cells and thereby greater variation of agonist-induced responses are observed. The variation in cellular responses has been well-characterized in slices prepared from male mice (Sánchez-Cárdenas and Hernández-Cruz, 2010; Durán-Pastén and Fiordelisio, 2013) where GnRH induces a variety of Ca^{2+} responses including biphasic, oscillatory and transient Ca^{2+} patterns (Fig. 3). The observations made by Sánchez-Cárdenas and Hernández-Cruz (Sanchez-Cardenas and Hernandez-Cruz, 2010) suggest that the gonadotropes can be divided into three different populations depending on the GnRH induced responses. Interestingly, steroid feedback changes the proportion of the three gonadotrope cell populations. Electrophysiological recordings of the membrane potential in genetically labeled male mice gonadotropes have also confirmed several different responses to GnRH (Wen et al., 2008). However, more studies are required to identify whether the different Ca^{2+} responses relate to electrophysiological responses.

As mentioned, in addition to internal Ca^{2+} stores, extracellular Ca^{2+} can contribute to the intracellular Ca^{2+} dynamics, both by directly stimulating hormone release and indirectly by replenishing intracellular stores. Similar to neurons, hormone producing cells in the pituitary are electrically excitable and can fire action potentials. In mammals we can grossly divide the hormone secreting cells into two types based on their action potential firing properties: those that mainly fire single spikes (action potentials) with low frequencies (< 1 Hz), and those that fire bursts of spikes (where the oscillating membrane potential produces periods with high frequency firing followed by quiescent periods). Gonadotropes and corticotropes typically fire single spike action potentials, at a frequency of around 0.7 Hz for gonadotropes and around 0.4 Hz for corticotropes. On the other hand, lactotropes and somatotropes have intrinsic burst-like firing properties in cell culture, and can show a pseudo plateau with superimposed spikes of action potentials, which sufficiently elevate $[Ca^{2+}]_i$ for hormone release (Stojilkovic et al., 2005b).

These action potentials are generated by voltage gated channels

including channels permeable for Na^+, Ca^{2+}, K^+ and Cl^- (see review (Stojilkovic et al., 2010)). However, the ion channel composition of the plasma membrane varies markedly between cell types as well as spatially and temporally within cells. In addition, the role played by the channels seems to be species dependent. Despite the presence of voltage gated Na^+ channels in gonadotropes, blocking these channels does not affect their firing properties in rat primary cell culture (Chen et al., 1989) while they are required for generating spontaneous action potentials in ovine gonadotropes (Heyward et al., 1995). In addition, pituitary endocrine cells possess voltage gated Ca^{2+} channels that are important for generating action potentials (Guérineau et al., 1991; Van Goor et al., 2001a). The presence of voltage gated Ca^{2+} channels allows the cells to regulate Ca^{2+} influx and thus the cytosolic Ca^{2+} signaling by modulating action potential shape and frequency.

Still, the single spike firing pattern with low frequency (around 1 Hz) is not sufficient to elevate the $[Ca^{2+}]_i$ required for releasing hormones into circulation. However, recordings of single cells (undefined type) in pituitary slices demonstrate that single spike action potentials generate small membrane oscillations with superimposed spike trains in guinea pig (Bonnefont and Mollard, 2003) that could potentially elevate $[Ca^{2+}]_i$ to levels required for hormone release. However, more experimental testing combining electrophysiology with Ca^{2+} imaging is necessary before conclusions can be made on the possible biological function of these bursts.

Several studies aimed to elucidate the mechanisms behind bursting vs single spike firing patterns of mammalian pituitary cells suggest that the pattern is a result of the cellular ion channel composition and properties. Particular focus has been on the Ca^{2+} activated K^+ channels (K_{Ca}) and their role in controlling pituitary excitability and secretion (Kukuljan et al., 1992; Van Goor et al., 2001b; Stojilkovic et al., 2005b; Duncan et al., 2015). Biophysical properties, localization and composition of the different K_{Ca} on the plasma membrane are important in fine-tuning the cellular behavior. Big/large conductance K_{Ca} (BK) channels are largely expressed in somatotropes, corticotropes, and lactotropes while small conductance K_{Ca} (SK) channels are mainly expressed in gonadotropes (Stojilkovic et al., 2005b; Duncan et al., 2015). SK channels in mammalian gonadotropes are in close proximity of ER release sites and are responsible for hyperpolarizing the membrane following agonist stimulation and IP3 induced elevation in $[Ca^{2+}]_i$. Experimental evidence also suggests that not only the composition of K_{Ca} contributes to fine-tuning the electrophysiological properties of gonadotrope cells, but in fact, most of the ion channels expressed by the cells are subject to modulation by auxiliary subunits as well as a plethora of direct and indirect feedback mechanisms (see review (Stojilkovic et al., 2010)). As an example, estrogen has been shown to transiently increase the Ca^{2+} current as well as the delayed K^+ currents in ovine gonadotropes (Heyward and Clarke, 1995; Cowley et al., 1999). In mice gonadotropes, however, estrogen did not affect the delayed outward K^+ current but rather inhibited the transient outward K^+ current (Waring and Turgeon, 2006). In addition, the transient Na^+ current was shown to be activated at lower membrane potentials following pretreatment with estrogen. Thus, mouse gonadotropes pretreated with estrogen require less membrane depolarization to trigger action potentials and thereby fire sooner compared to untreated cells. Therefore, estrogen facilitates action potential firing in mouse gonadotropes both by inhibiting the transient outward K^+ current and by activating the transient Na^+ incurrent. Opposite effects of estrogen on ionic currents have also been observed within the same species. For instance, it stimulates BK channel currents but inhibits SK channel currents in mice gonadotropes (Waring and Turgeon, 2008). This differential regulation was demonstrated to facilitate LH release.

2.2.2. Fish

In general, we find that fish and mammals share common properties and mechanisms mediating hormone secretion. Gonadotrope cells in fish pituitary are electrically excitable and have the capacity to fire action potentials. Moreover, an intricate interplay between ER Ca^{2+} release and Ca^{2+} influx across the cell membrane to regulate hormone secretion has been investigated in several fish species. The species include Mozambique tilapia (Seale et al., 2004; Xu and Cooke, 2007; Bloch et al., 2014), Atlantic cod (Haug et al., 2007; Hodne et al., 2013), goldfish (Van Goor et al., 1996; Chang et al., 2000; Yu et al., 2010) and medaka (Strandabo et al., 2013b; Karigo et al., 2014; Fontaine et al., 2018; Halnes et al., 2019; Hodne et al., 2019).

While agonist induced $[Ca^{2+}]_i$ oscillations such as the ones found in mammalian pituitary cells have not been reported in fish, gonadotrope cells have been shown to display a biphasic $[Ca^{2+}]_i$ response to Gnrh in goldfish, Atlantic cod and medaka. This biphasic response is dependent on both intracellular stores and extracellular Ca^{2+} influx. Following Gnrh stimulation, a first phase hyperpolarization is observed in Lh cells and reflects the release of Ca^{2+} from internal stores and subsequent elevation of $[Ca^{2+}]_i$, activating K_{Ca} channels at the cell membrane. In goldfish, it has been demonstrated that $[Ca^{2+}]_i$ increases due to activation of both IP3R and RyR, and allows gonadotropin secretion. Interestingly, these two ER Ca^{2+} channels are differentially activated by the two goldfish isoforms of Gnrh (Chang et al., 2000). The second phase of the response is characterized by both increased firing frequency of action potentials and a broadening of each spike. This has been observed in both primary cell culture and brain-pituitary slices (Ager-Wick et al., 2018; Fontaine et al., 2018; Hodne et al., 2019). These action potential modulations facilitate the influx of Ca^{2+} and thereby hormone release.

The agonist induced-elevation in $[Ca^{2+}]_i$ in Atlantic cod and medaka Lh cells also induces changes in membrane potential. Similar to mammals, fish gonadotrope cells rely on ion channels, including Ca^{2+}, K^+, Na^+, and ion exchangers, to regulate cell excitability and Ca^{2+} influx. Ion channel composition varies within a cell population and between different fish species. For instance, goldfish gonadotropes lack SK channels which are important in regulating the excitability of mammalian gonadotropes (Van Goor et al., 1996). In addition, perforated current clamp recordings of dispersed goldfish pituitary cells, presumed to be gonadotropes based on morphological characteristics, did not detect any changes in membrane potential following Gnrh stimulation (Johnson et al., 2000). In contrast, SK channels were found in Atlantic cod and medaka gonadotropes, which also have BK channels as well as voltage gated Na^+, K^+, and Ca^{2+} channels (Hodne et al., 2013; Strandabo et al., 2013b). In medaka, BK channels are highly expressed in Lh cells (Strandabo et al., 2013b), while SK channels represent the main K_{Ca} in mammalian gonadotropes. BK channels in medaka Lh cells exert effects opposite of those in mammalian somatotropes, and blocking them transform the action potentials from spiking to plateau-like potentials (Halnes et al., 2019). In addition, similar to ovine gonadotropes, voltage gated Na^+ channels (tetrodotoxin-sensitive) are essential to initiate action potentials in medaka (Halnes et al., 2019) and Atlantic cod (Hodne et al., 2013). Indeed, voltage gated Na^+ channels are absent in the gonadotropes that do not fire action potentials in Atlantic cod (Hodne et al., 2013).

While most of the studies have been performed on dissociated gonadotrope cells several studies have been performed on brain and pituitary sections (Levavi-Sivan et al., 2005; Hodne et al., 2019) thus allowing to investigate gonadotrope cell response to Gnrh in a more intact environment. Interestingly, the study performed in adult female medaka revealed that Fsh cells do not express Gnrhr, and do not respond to Gnrh1 *in vitro* after dissociation. However, they respond to Gnrh1 with increased $[Ca^{2+}]_i$ and action potential firing frequency in brain-pituitary slice preparations (Hodne et al., 2019). This study also demonstrated that the contradictory results between cell culture and brain-pituitary slices can be explained by cell–cell coupling. These couplings generate homo- and heterotypic networks between the gonadotrope cells (discussed further in detail in chapter 4), which allow Lh cells to relay information to Fsh cells such as G-protein induced changes in membrane potential. Therefore, gonadotrope cell activity

seems dependent on networks and cellular environment.

Finally, there is some evidence that plasticity in terms of channel expression and density may explain some of the dramatic seasonal and daily changes in circulation gonadotropin levels in fishes. For example, studies in Atlantic cod showed that both BK- and SK- channel mRNA levels and their corresponding ionic currents vary during the reproductive seasons, thus differentially regulating the action potential firing properties in Fsh and Lh cells (Hodne et al., 2013). This change in channel composition leads to plasticity of gonadotrope cell activity. However, the mechanisms behind how pituitary endocrine cells regulate the different ion channels and modulate the channel properties in response to environmental cues are poorly understood in fish. Important remaining questions include how do steroids in combination with G-protein activation modulate ion channels, is the modulation inhibitory or excitatory, and at what level does the modulation occur (gene expression level, or modulation of the channel itself through phosphorylation or changes in subunit composition).

2.3. Summary

In this chapter we have described significant changes in cellular sensitivity to ligand related to important biological events occurring during the life cycle of an animal such as sexual maturation but also short-term changes such as daily rhythms. Indeed, hormone synthesis and secretion have both been shown to rapidly change, influenced by endocrine signals originating from a variety of tissues including brain, peripheral organs and the pituitary itself. While rapid changes in hormone gene expression most likely result from variations in cellular activity, when observing changes over longer periods of time (e.g. during sexual maturation), this assumption should be taken with more caution as the techniques commonly used cannot take into account changes in the number hormone producing cells (e.g. through phenotypic conversion). Future studies using a combination of several techniques such as qPCR analysis in parallel with cell counting via *in situ*- or immuno-hybridization, or single cell transcriptomic analysis, are thus needed to investigate whether or not these changes are due to increased number of cells, increased cellular activity, or a combination of both.

We have seen that the main mechanisms controlling gonadotrope cell activity have mostly been conserved between mammals and fish. However, much less is known in fish compared to in mammals, which may be due at least in part to the high diversity of fish species. Indeed, the receptors involved in the control of hormone synthesis and secretion have multiple paralogs in most fish species. Some paralogs have been shown to be differentially expressed, spatially and temporally, suggesting that they may have distinct functions. However, information regarding the specific roles of the different receptor paralogues in teleosts are still fragmentary. To determine their roles, more information on their cellular localization within the pituitary gland is needed. This may be achieved using recently developed fluorescent *in situ*- and immuno- hybridization protocols that allow the simultaneous staining of multiple mRNA and protein targets. These techniques, combined with improved confocal microscopy to remove the noise deriving from overlapping cellular layers, allow the exact localization of specific receptor paralogues in different cell types, and can provide important information regarding the regulation of pituitary functions.

Hormone secretion, controlled by $[Ca^{2+}]_i$, ultimately depends on the type, location, and abundance of different ion channels. These characteristics vary in time and among cells within an endocrine population, thus providing different electrophysiological properties to the cells and different responses to the same stimulus. So far, while powerful new tools, such as transgenic lines that specifically label gonadotrope cells, and fluorescent calcium reporter proteins to trace calcium activity in ex-vivo tissues, have been employed, their use to investigate gonadotrope cell activity has been limited to a few species. Therefore, our understanding of the biophysical properties that regulates secretion is limited. We still lack a detailed understanding of ion channel dynamics but novel tools that combine electrophysiology with single-cell transcriptomics should help us to understand the intricate nature of hormone secretion from the pituitary.

3. Plasticity at the population level: reorganization of pituitary cell composition

When increasing the hormone production of each cell in the population is not sufficient to raise the plasma level of hormone according to the present needs, other means are required. One strategy is to increase the number of cells producing the required hormone thus leading to a change in the composition of cell types in the pituitary. This has been observed in mammals as well as in fish during puberty. For example, the number of gonadotropes in the pituitary varies over the estrous cycle in several mammals including rats (Childs et al., 1987) and ewes (Taragnat et al., 1998; Molter-Gerard et al., 2000). Similarly, in fishes, the number of gonadotropes in the pituitary increases during puberty in medaka (Fontaine et al., 2019a,b) and in male African catfish, *Clarias gariepinus* (Cavaco et al., 2001). In tilapia, Fsh cell hyperplasia has also been demonstrated in dominant compared to in subordinate males (Golan and Levavi-Sivan, 2013).

Different mechanisms to increase the number of specific hormone-producing cells in the pituitary include: i) proliferation and differentiation of pituitary progenitor cells, ii) mitosis of already differentiated hormone producing cells, and iii) recruitment of existing pituitary cells through phenotypic conversion.

3.1. Proliferation of progenitor cells

Embryonic stem cells are defined as totipotent cells able to generate all cell types that constitute all developed tissues (Florio, 2011). These undifferentiated cells are able to self-renew and to generate different multipotent progenitor cells, which can divide and differentiate into a limited number of cell types according to the specific tissue of origin (Potten and Loeffler, 1990). Multipotent progenitor cells are found in several tissues in adults, in both mammals and fishes (Duan et al., 2008; Chapouton and Godinho, 2010). These adult multipotent progenitor cells reside in specific areas ('niches') in the tissues that support and regulate their proliferation (Greco and Guo, 2010) and are involved in tissue maintenance and repair. In both the mammalian and teleost pituitary, several studies have demonstrated that such progenitor cells persist in adult stages as discussed below.

3.1.1. Mammals

Nolan et al. reported that a group of non-hormone producing pituitary cells proliferated and differentiated into corticotropes or gonadotropes, after adrenalectomy or gonadectomy in adult male rats (Nolan et al., 1998; Nolan and Levy, 2006). Using the multipotent progenitor cell marker Sox2 (Fauquier et al., 2008b; Kelberman et al., 2009), the specific niches of multipotent progenitor cells were localized in mice (Fauquier et al., 2008a; Fauquier et al., 2008b) and rats (Chen et al., 2013) (Fig. 4A), in a concentrated layer lining the mammalian pituitary cleft, the intraglandular structure at the border of the neurohypophysis and adenohypophysis, with a few additional cells scattered in the adenohypophysis.

3.1.2. Fish

Sox2 has also been shown to be a multipotent progenitor cell marker in the fish brain (Alunni et al., 2010) and retina (Lust and Wittbrodt, 2018). In the pituitary, Sox2-immunopositive cells have been described in only one fish species, the medaka (Fig. 4B) (Fontaine et al., 2019b). In this species, Sox2-immunopositive cells are located at the junction of the neurohypophysis (where the neuronal projections from the hypothalamus enter the pituitary) and the adenohypophysis, a region anatomically similar to the mammalian pituitary cleft. A few more cells were also observed scattered throughout the adenohypophysis.

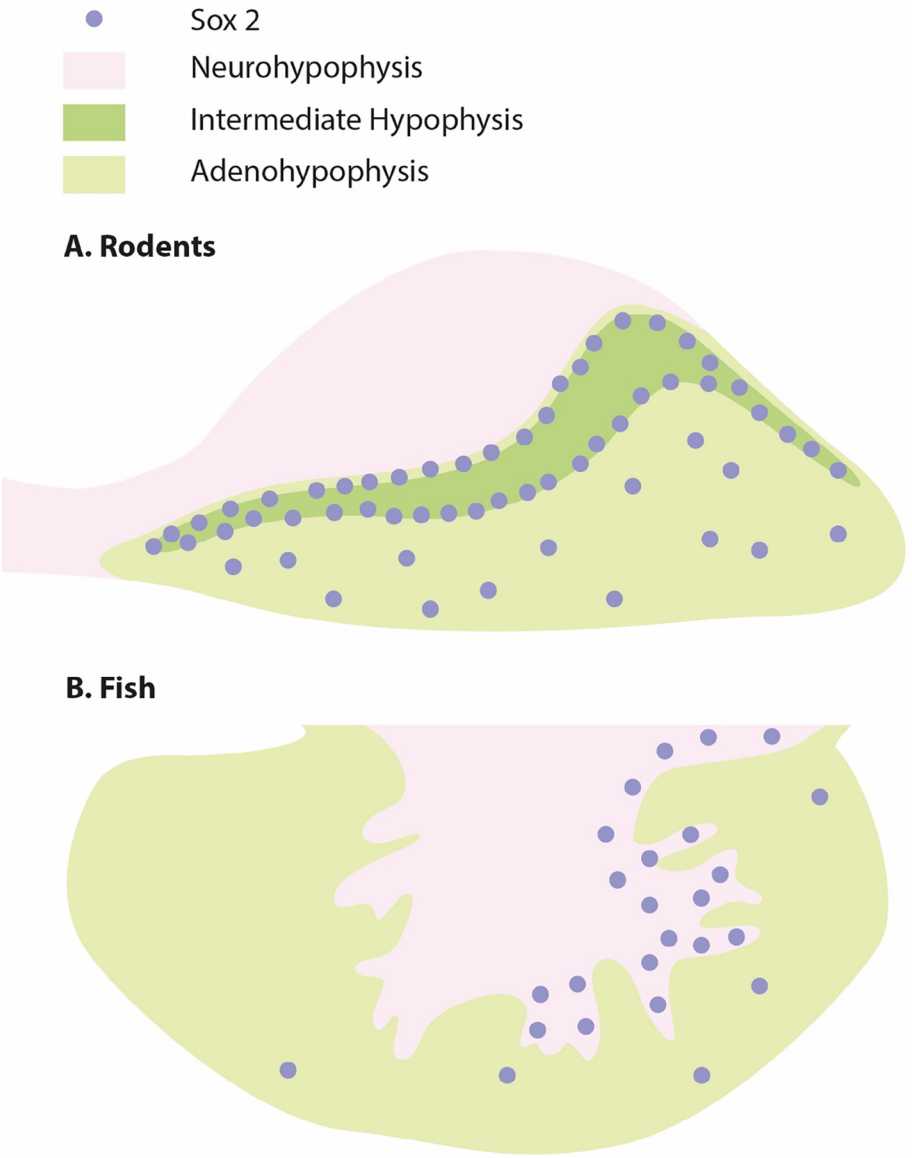

Fig. 4. Localization of the Sox2 immunopositive cells in the pituitary from mammals (A) and fish (B). Modified according to (Chen et al., 2013) for mammals and (Fontaine et al., 2019b) for fish. In mammals Sox2 positive cells are localized in a concentrated layer lining the mammalian pituitary cleft (the intraglandular structure), with a few additional cells scattered in the adenohypophysis. In fish, Sox2 positive cells are also localized at the border of the neurohypophysis and adenohypophysis, with a few additional cells scattered in the adenohypophysis.

Whether Sox2-positive cells are found in the pituitary of all fish species, and whether they are truly multipotent progenitor cells remain to be established. Also, while several studies suggest that proliferation and differentiation of progenitor cells plays a major role in pituitary plasticity in mammals (Florio, 2011), the importance of this mechanism in fish pituitary plasticity is presently unknown and warrants further investigation.

3.2. Mitosis of hormone producing cells

Another means to change the number of a specific pituitary cell population is through mitosis of the hormone producing cells themselves. Indeed, like stem cells, fully differentiated hormone-producing cells retain the capacity to divide and therefore to contribute to pituitary cell hyperplasia in the adult pituitary.

3.2.1. Mammals

In the mammalian pituitary, proliferation of hormone producing cells has been observed in different life stages and for different hormone producing cell types, including gonadotropes (Taniguchi et al., 2002). The number of mitotic gonadotropes was shown to increase up to six times in castrated rat pituitaries (Sakuma et al., 1984). This suggests a large contribution of gonadotrope mitosis to their proliferation. In contrast, in adrenalectomized rats, although the number of corticotropes increased, most dividing cells were not ACTH immunopositive (McNicol and Carbajo-Perez, 1999) suggesting a minimal role of corticotrope mitosis in their proliferation. Thus, the importance of this mechanism seems to be cell type dependent.

3.2.2. Fish

In fish, proliferation of hormone producing cells has also been observed in the adult pituitary. In medaka for example, using a combination of PCNA staining and BrdU exposure, it was demonstrated that both Fsh and Lh cells can divide (Fontaine et al., 2019a; 2019b). In the first study, it was also found that, unlike in mammals, a significant proportion (up to 60%) of the dividing cells in the pituitary were Lh

cells, suggesting the importance of Lh gonadotrope expansion in fish. However, a study in juvenile male African catfish (Cavaco et al., 2001) found no evidence of gonadotrope proliferation despite increasing numbers of gonadotropes. Therefore, the role of gonadotrope cell mitosis plays in their proliferation seems to depend on the species and the physiological status of the animal.

3.3. Recruitment of existing pituitary cells through phenotypic conversion

A third mechanism to increase the number of cells to produce a particular hormone is to recruit existing pituitary cells. These cells could be quiescent cells which do not constitutively express the hormone but are recruited when increased hormone production is required. But, how can these dormant cells be identified when they are not producing any hormone? The investigation of such cells would be technically challenging, requiring *in vivo* temporal analysis of their activity and hormone production profile over time. In addition, a problem of definition also rises here. According to Pogoda and Hammerschmidt (2009), endocrine cells are defined as cells that produce a specific hormone mRNA or protein. This definition would exclude quiescent cells, i.e., not producing hormone at the time of observation. For both reasons the role of these quiescent, potentially hormone producing, cells has been poorly examined. Here, we will focus on phenotypic conversion of differentiated cells, i.e., the transformation of cells from one hormone type to another thereby changing their secretory capacity, a process termed transdifferentiation (Horvath et al., 1990).

3.3.1. Mammals

In mammals, observations of phenotypic conversion have been described for several hormone producing pituitary cell types. It is interesting to note that so far, observations of transdifferentiation have been mostly observed between cells types belonging to the same lineage and thus sharing an important part of their differentiation pathway. For example, somatotropes, lactotropes and tyrotropes, which belong to pit1 derived cell lineage (Haston et al., 2018), can interconvert. Somatotropes have been found to be able to reversibly convert into mammotropes in rats (Porter et al., 1991), and somatotrope conversion to thyrotropes has been described, in both hypothyroid rats (Horvath et al., 1990) and in humans (Vidal et al., 2000). Both somatotropes and mammotropes have been found to convert into mammosomatotropes in cattle (Kineman et al., 1991) and in human (Vidal et al., 2001) during pregnancy and lactation (Frawley and Boockfor, 1991). However, there are also reports of GnRH-induced transdifferentiation of rat somatotropes into somatogonadotropes *in vitro* (Childs and Unabia, 1997); importantly, these cell types belong to two different lineages (Prop1-positive cells for somatotropes and Sf1-positive cells for gonadotropes (Haston et al., 2018)) and have different molecular composition as well as different firing properties (Stojilkovic et al., 2005a). The specific molecular changes in these cells and whether this transformation extends to the electrical properties and firing properties characteristic of gonadotropes remain to be elucidated.

Mammalian gonadotropes also show high plasticity. Transdifferentiation to corticotropes in gonadotropic adenomas has been documented, although this phenomenon is likely rare (Ikeda et al., 1995; Egensperger et al., 2001). More relevant to reproductive physiology, mammalian gonadotropes can change between the more typical bi-hormonal phenotype and a mono-hormonal phenotype. For example, in the ewe, there is evidence that bi-hormonal cells (producing both FSH and LH) may switch to a mono-hormonal phenotype in sheep (most of which produce only LH) (Taragnat et al., 1998). In rhesus monkey, it appears that mono-hormonal FSH cells may switch to the bi-hormonal phenotype during puberty (Meeran et al., 2003). These changes between the different subtypes of gonadotropes is therefore likely possible because they share most of their differentiation paths (Haston et al., 2018).

3.3.2. Fish

Much less is known about transdifferentiation in fishes, and most of the observations concern Lh and Fsh cells, which also share most of their differentiation pathways in fish; indeed the pathways are very similar to that of mammalian gonadotropes (Weltzien et al., 2014). In juvenile African catfish, the number of cytologically mature gonadotropes was seen to increase during puberty. As the authors did not observe any cell proliferation, they suggested that existing pituitary cells may have been converted to mature gonadotropes (Cavaco et al., 2001). In addition, while fish gonadotropes are typically mono-hormonal, bi-hormonal cells have been described in several species including the Mediterranean yellowtail (*Seriola dumerilii* (Hernandez et al., 2002), zebrafish, tilapia (Golan et al., 2014), European hake (*Merluccius merluccius* (Candelma et al., 2017) and medaka (Fontaine et al., 2019a). In medaka, Fontaine and coworkers found that some Fsh cells began to produce Lh in cell culture, thus confirming the capacity of fish gonadotropes to change phenotype (Fontaine et al., 2019a). However, transdifferentiation or phenotypic conversion of other pituitary cell types has not yet been reported, perhaps due to limited study. New technologies such as single cell transcriptomics should soon allow us to provide more information on the plasticity of gonadotropes and other cell types in the fish pituitary. Furthermore, the role and importance of transdifferentiation in overall pituitary plasticity requires further study.

3.4. Factors controlling pituitary cell population plasticity

It is now clear that the relative number of gonadotropes fluctuates to meet the demands of different physiological states and life stages, particularly during growth, puberty, seasonal maturation or pregnancy. While the mechanisms allowing pituitary plasticity at the population level are beginning to be elucidated, their regulation remains poorly understood.

3.4.1. Mammals

In mammals, marked diurnal changes in the mitotic rate of pituitary cells have been reported in rats (Nouet and Kujas, 1975) suggesting that melatonin may play a role in pituitary plasticity. For gonadotrope plasticity, factors known thus far to play a role in this plasticity include GnRH, sex steroids, and paracrine signals. As early as 1957, experiments of pituitary grafts first transplanted to the kidney and later retransplanted to the median eminence clearly demonstrated that brain factors were responsible for the proper re-establishment of functional pituitary gonadotropes, thyrotropes and corticotropes in rats (Nikitovitch-Winer and Everett, 1957, 1959). Since then, GnRH has been shown to suppress proliferation in a gonadotrope-derived cell line (LbetaT2) (Miles et al., 2004), but to significantly increase proliferation in female mice pituitary cell cultures (Lewy et al., 2003). *In vivo*, GnRH was shown to stimulate gonadotrope cell proliferation in castrated male rats (Sakai et al., 1988). In addition, GnRH has been shown to mediate changes in pituitary gonadotrope subtypes. It promotes phenotypic conversion of mono-hormonal FSH cells into bi-hormonal cells *in vitro* in rats (Childs, 1985) while it increases the number of FSH-monohormonal and LH-monohormonal cells, and decreases the number of bi-hormonal gonadotropes *in vivo* in sheep (Taragnat et al., 1998).

Steroids, particularly sex steroids, also play important roles in gonadotrope plasticity in mammals. In rats for example, mitotic LH cells drastically increased after castration in males (Sakuma et al., 1984), and ovariectomy in females (Smith and Keefer, 1982), thus suggesting that steroids suppress LH cell proliferation.

Finally, paracrine signals have also been described to affect the differentiation of gonadotrope cells in the mammalian pituitary. Indeed the work of Denef and coworkers, in which dissociated rat pituitary cells were separated and cultured according to their size (Denef et al., 1976), revealed that the percentage of bi-hormonal gonadotropes and their response to GnRH were different depending on the cell type composition of the culture (Denef et al., 1978; Denef, 1980). This study

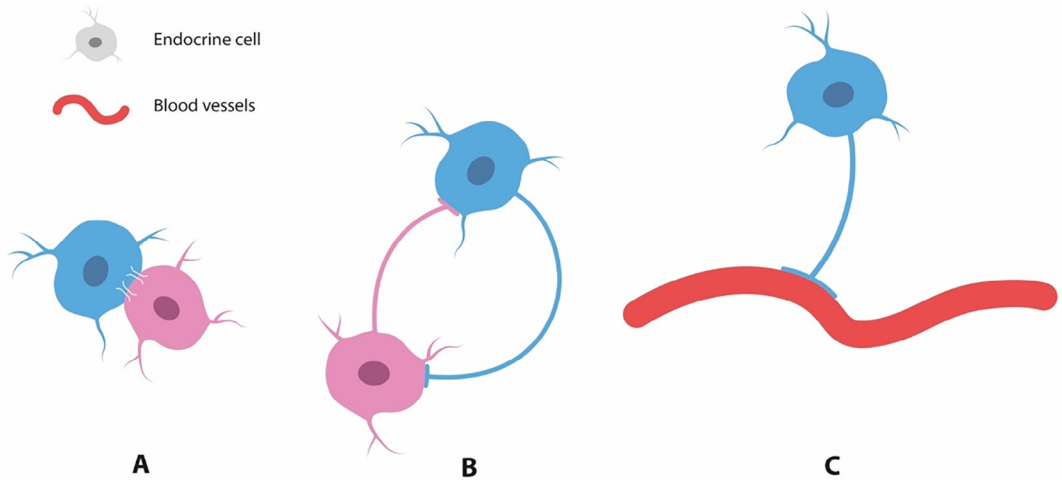

Fig. 5. Schematic representation of three different ways pituitary endocrine cells interact with their environment. (A) Endocrine cells with soma-soma connections, making either homotypic or heterotypic networks, (B) Endocrine cell extensions to connect to other cells, for communication or for migration and clustering, and (C) Endocrine cell extensions toward blood vessels, for receiving signals from the circulation or releasing hormones to the circulation.

clearly demonstrated that signals from other pituitary cells, later identified and found to come from other endocrine cells (for review (Denef, 2008)) and folliculostellate cells (Bilezikjian et al., 2003), contribute to the regulation of gonadotrope cell plasticity.

3.4.2. Fish

Gnrh and estradiol appear to also affect gonadotrope proliferation in fish. Indeed, in medaka pituitary cell cultures, Gnrh promotes phenotypic conversion of some Fsh cells into Lh or bi-hormonal cells (Fontaine et al., 2019a). In contrast to mammals, where steroids seem to inhibit gonadotrope cell proliferation, estradiol (and testosterone via its aromatization into estradiol) promotes proliferation of both Fsh and Lh cells in the medaka pituitary (Fontaine et al., 2019a). Moreover in juvenile male African catfish, estradiol appeared to promote phenotypic conversion of some existing cells from unknown identity into gonadotropes (Cavaco et al., 2001; Fig. 5A). However, sex steroid effects are known to diverge depending on the species and the physiological status of the fish (Yaron et al., 2003; Zohar et al., 2010), preventing any conclusions that steroids generally promote gonadotrope proliferation.

Regarding the role of paracrine signals on the plasticity of pituitary cell populations, nothing is known in fish. However, recent findings showed that Fsh cells which do not possess Gnrh receptors in adult female medaka pituitary (Hodne et al., 2019), start to express them after dissociation and long-term culture (Fontaine et al., 2019a). This seems then to allow Fsh cells to produce Lh when activated by Gnrh in cell culture. These observations suggest that a paracrine signal inhibits Gnrh receptor expression in Fsh cells and maintains their monohormonal identity.

3.5. Summary

In this chapter we have described significant changes in pituitary composition related to important biological events occurring during the life cycle of an animal, in a similar way in both mammals and fish. Indeed, the number of gonadotropes has been found to vary according to needs through three mechanisms: proliferation and differentiation of progenitor cells; proliferation of the hormone producing cells themselves; and phenotypic conversion of differentiated pituitary cells (transdifferentiation). So far, these three mechanisms have been found to be controlled by hypophysiotropins such as Gnrh, sex steroids (mainly estradiol), and by paracrine signaling. While many similarities have been observed between mammals and fishes, we can clearly see that there are also differences certainly related to their different life histories. In addition, the lack of information in fish compared to in mammals is apparent, perhaps due to the limited number of research teams working on the fish pituitary. However, we expect that the improvement of genetic tools- such as transgenic lines in which specific pituitary cell types can be identified, in addition to Crispr/Cas9, and single-cell transcriptomics, in combination with advanced imaging techniques such as confocal imaging, will greatly advance research on the plasticity of the different cell types, the mechanisms responsible, and the molecular pathways underlying their regulation. Future studies should aim to clarify the roles and importance of these three different mechanisms in the fish pituitary during puberty and seasonal reproduction.

4. Plasticity at the structural level: intercellular networks and migration

The hormone-producing cells in the pituitary do not operate in isolation, but rather have functional anatomical contacts with other endocrine and non-endocrine pituitary cells. There is increasing evidence in both fish and mammals that these contacts can serve to coordinate function among the cells. There is also increasing evidence that such cell–cell contacts can change, as cells proliferate, migrate or modify cellular extensions. Since the degree of synchronicity of a cell population would increase with the number of functional connections in a network, the ability to expand the network could allow an organism to meet the changing needs for that particular hormone. Indeed, there is evidence for plasticity of such networks.

4.1. Intercellular pituitary networks

It has become increasingly clear the last few years that in mammals, several pituitary cell types connect with each other in complex homotypic and heterotypic networks (Bonnefont et al., 2005; Budry et al., 2011; Mollard et al., 2012). These networks enable a very efficient level of secretion control by permitting synchronization of release. Similar networks, and similar functions, have been more recently described in fish (Golan et al., 2016b; Grønlien et al., 2019; Hodne et al., 2019).

4.1.1. Mammals

In mammals, all anterior pituitary endocrine cells except thyrotropes are known to form homotypic and/or heterotypic cellular networks. In fact, only the thyrotropes seem not to form extensive networks (Hodson et al., 2015). Gonadotropes form both homotypic and heterotypic cellular networks in mammals (Budry et al., 2011; Alim et al., 2012; Edwards et al., 2017). Interestingly, the gonadotropes,

which differentiate relatively late during development, seem to be dependent on a preexisting corticotrope network to construct their own homotypic network, mostly in close proximity to capillaries. Furthermore, gonadotropes also seem to form heterotypic networks with lactotropes (Seuntjens et al., 1999).

In mice, most or all somatotropes, the most abundant endocrine cell type in the pituitary, are connected by adherens junctions into a complex homotypic 3D network (Bonnefont et al., 2005). Lactotropes also form functional and structural homotypic networks (Hodson et al., 2012b). Importantly, these networks display a high degree of plasticity, adapting to different physiological challenges.

Although the focus of this review is on pituitary endocrine cells, it is worth mentioning another wide-ranging, complex cellular network in the pituitary, consisting of the non-endocrine folliculostellate cells. Folliculostellate networks have been described in mammals as stretching through large parts of the pituitary, communicating with different endocrine cell populations, and efficiently transferring signals over long distances via gap junctions (Fauquier et al., 2001). Thus, this network may coordinate hormone secretion and also be subject to plasticity.

4.1.2. Fish

Similar endocrine networks are also being discovered in teleosts. Indeed, Lh cells have been described to form networks in both tilapia (Golan et al., 2016b) and medaka (Grønlien et al., 2019). In addition, heterotypic networks between Lh and Fsh cells are also formed in medaka (Hodne et al., 2019).

Functional folliculostellate networks have also been described in one species, the tilapia (Golan et al., 2016a). In contrast to the mammalian pituitary research, where the somatotrope network has received the most attention, in fish, research has focused on the gonadotrope network as will be described in the following sections.

4.2. In the networks, cells are either connected via extensions or soma-soma contacts

Among groups of cells situated in densely packed clusters, it is easy to imagine functional connections formed at soma-soma contact points, for instance via gap junctions (Fig. 5A). However, for less densely arranged cells cellular extensions may be required.

While it was previously held that intercellular connections via long cellular extensions was a trait belonging primarily to neurons, the emerging view is that a plethora of different, non-neuronal cell types also form extensions that connect and communicate with other cells (Kornberg and Roy, 2014) (Fig. 5B). Such cell-to-cell connections can be either a direct cytosolic connection via membrane fusion or gap junctions (open ended), or a physical connection of membrane components without connected cytoplasm (closed-ended) (Roy et al., 2011; Galkina et al., 2013; Sherer, 2013; Eom et al., 2015; Kornberg, 2017).

4.2.1. Mammals

In mammals, the gonadotrope networks are formed partly in clusters and strings, where functional soma-soma contact points are likely, and partly by extensions (Budry et al., 2011; Alim et al., 2012; Edwards et al., 2017). Expression of intracellular adhesion molecule-5 (Icam5), known to participate in synapse formation between axons and dendritic spines in the telencephalon, has also been found in some gonadotropes, leading Le Tissier and Mollard to speculate that it may play a role in the formation of homotypic gonadotrope networks (Le Tissier and Mollard, 2016). Mammalian somatotropes seem to form their extensive networks with soma-soma contacts (Bonnefont et al., 2005). This is not surprising, since they are the dominating cell type in the anterior pituitary, and thus somatotropes have a high chance of bordering other somatotropes. In contrast, corticotropes display several thin extensions in the intact pituitary, where they not only contribute to homotypic network formation, but also extend toward local blood vessels (Westlund et al., 1985; Childs et al., 1989; Budry et al., 2011).

4.2.2. Fish

In zebrafish, Fsh-producing gonadotropes are loosely grouped and situated close to blood vessels, while Lh-producing gonadotropes are densely packed such that only some Lh cells are in close contact with blood vessels (Golan et al., 2015). In the Mediterranean yellowtail, Lh cells are also found in compact clusters or strands, while Fsh cells form smaller clusters or appear alone (Pilar Garcia Hernandez et al., 2002). Likewise, in the medaka pituitary, Lh cells are clustered tightly (Hildahl et al., 2012; Fontaine et al., 2019b), but, similar to mammalian gonadotropes, form extensions that may be used in network formation (Strandabo et al., 2013a; Grønlien et al., 2019). It has recently become clear that medaka Fsh cells form similar extensions (Fontaine et al., 2019a). These extensions are strikingly different from those seen in mammalian gonadotropes, as they are substantially longer, display varicosity-like swellings, contain both microtubule and actin cytoskeletal elements, and often branch. In African catfish (*Clarias gariepinus*), Lh-positive gonadotropes also form long extensions that may contact other gonadotropes (Schulz et al., 1997; Dubois et al., 2000). Interestingly, the degree of clustering seems to vary during development and puberty, suggesting plasticity.

Analogous structures have been reported in other pituitary cell types in fishes, although not as extensively described as the gonadotrope extensions. Thyrotrope extensions have been reported in Atlantic halibut (*Hippoglossus hippoglossus*) (Weltzien et al., 2003) and the chondrostean species *Acipenser naccarii* (which did not display extensions on Lh-positive cells) (Grandi and Chicca, 2004). Corticotrope processes have been reported in the gilthead sea bream (*Sparus aurata*) (Villaplana et al., 2002) and in the nine-spined stickleback (*Pungitius pungitius*) (Benjamin, 1982), the latter containing secretory granules. Lastly, small ciliated protrusions have been described in the anadromous alewife (*Alosa pseudoharengus*) (Betchaku and Douglas, 1981).

4.3. Cellular extensions facilitate clustering

To form and modify such elaborate networks, dynamic cellular extensions may be important. Growing extensions may recognize the correct cell to connect to, and either form a permanent connection, or maintain the contact while the connected cells migrate toward each other to form clusters with soma-soma contacts. While these events are still hypothetical, several lines of evidence support their occurrence, some of them presented below.

4.3.1. Mammals

That GnRH-stimulated gonadotropes form cellular processes has been known for a long time (Childs, 1985). GnRH-stimulation of gonadotropes also increases the number of cellular extensions (Navratil et al., 2007; Alim et al., 2012), and may also induce cell migration (Navratil et al., 2007; Godoy et al., 2011). Thus, increased GnRH signaling during puberty may better coordinate hormone release by promoting development of more efficient networks. Furthermore, Alim and colleagues have presented compelling evidence of spatial plasticity of the gonadotrope population in mice (Alim et al., 2012). Before puberty, gonadotropes were evenly distributed throughout large parts of the anterior pituitary, but always close to blood vessels. After puberty, the gonadotropes were more abundant in the rostral area than in other areas. Perhaps the most striking observation was the appearance of discrete string-like clusters of gonadotropes during lactation (see also (Edwards et al., 2017)). Thus, in contrast with the general view that the pituitary cell types are spread evenly throughout the mammalian adult pituitary, it is evident that at least gonadotropes may cluster after puberty, which could permit coordinated hormone release.

4.3.2. Fish

Unlike the adult mammalian adenohypophyis, in the teleost the

different endocrine cell types are clustered in different areas (Pogoda and Hammerschmidt, 2007; Musumeci et al., 2015). The spatial arrangement of the different cell types is more or less complete during the larval stage, and remains in place for the entire lifespan of the fish. We propose that at least for Lh-positive cells in medaka, both transient and permanent cellular extensions are important for the recognition and connection to homotypic cells in extensive networks (Grønlien et al., 2019). In primary cell cultures, the Lh cells migrate and form clusters after a few days, apparently aided by extensions. As in mammals, Gnrh increases formation of cellular extensions from the medaka Lh-gonadotropes. Whether similar movement or Gnrh-induced extension forming occur *in vivo* is not known. Furthermore, the majority of multipotent progenitor cells have been described in the dorsal but not the ventral part of the medaka pituitary where mature Lh cells are found (Fontaine et al., 2019b). Thus, before these multipotent progenitor cells differentiate into Lh cells, substantial migration must take place. Still, very little is known regarding whether specific organizational changes take place within the fish pituitary due to particular life-change events like puberty and seasonal maturation, smoltification and migration.

4.4. Networks facilitate hormone secretion

4.4.1. Mammals

Several of the homotypic networks in the mammalian pituitary are comprised of functionally connected cells which communicate via gap junctions (Hodson et al., 2015; Vitale and Pelletier, 2018). Such electrical connections between the gonadotropes permit synchronized gonadotropin release (Sanchez-Cardenas and Hernandez-Cruz, 2010; Gongrich et al., 2016). Furthermore, differential regulation of this electrical coupling may create different patterns of secretion between the sexes or between different life stages. The more cells that are connected electrically, the more efficiently a signal triggering hormone secretion may spread, favoring large, rapid changes in plasma Ca^{2+} concentration. The effect of coupling might not primarily be an increase in secretion as much as a sharpening of the hormone pulse, which may be important for downstream responses. Furthermore, releasing hormone-induced Ca^{2+} signals may last longer and amplify in cellular networks (Hodson et al., 2012a). Gongrich and colleagues showed that ablating the gap junction subunit Cx36 in mice reduced the amount of GnRH-induced LH (Gongrich et al., 2016). Dye transfer experiments indicate that lactotropes and somatotropes are also functionally connected in homotypic, plastic networks via gap junctions (Hodson and Mollard, 2013; Hodson et al., 2015). Lactating mice display a dramatically higher proportion of connected lactotropes, concurrent with the appearance of long-lasting Ca^{2+} plateaus and elevated plasma prolactin (Hodson et al., 2012b). Connected somatotropes exhibit synchronous Ca^{2+} pulses in response to growth hormone-releasing hormone (GHRH) (Sanchez-Cardenas et al., 2010). Interestingly, a larger proportion of the somatotrope population is connected via networks in males than in females, corresponding with a larger GH release in response to GHRH. Importantly, sex differences in GHRH-GH release are not seen in dispersed somatotropes, indicating the importance of cellular networks for robust hormone release.

Cellular extensions on gonadotropes may also facilitate hormone secretion by extending toward the pituitary blood vessels (Childs, 1985; Navratil et al., 2007; Alim et al., 2012). Alim and colleagues found that gonadotropes in pituitary slices grew new extensions, some of them toward blood vessels. Corticotropes may also display cellular extensions directed toward blood vessels (Itoh et al., 2000).

4.4.2. Fish

Like mammalian gonadotropes, fish gonadotropes also form cellular networks that permit intercellular communication through gap junctions (Golan et al., 2015; Golan et al., 2016b). In tilapia and zebrafish, Lh-producing gonadotropes are functionally coupled by gap junctions in soma-soma-contacts, forming a large, continuous network (Golan et al., 2016b). Uncoupling gap junctions with meclofenamic acid greatly reduced Lh release, indicating the importance of electrical coupling for the total hormone release. Fsh gonadotropes appear to form a looser network via cellular extensions, rather than via gap junctions, and Fsh release was not affected by the gap junction uncoupler. Since only 20% of the Lh cells are in close proximity to a Gnrh neuron, while most Fsh cells are, it follows that Lh cells may be more dependent on coordinating the Gnrh-induced Ca^{2+} signals than the Fsh cells (Golan et al., 2015). In the medaka Lh gonadotropes, Ca^{2+}-signals transfer between cells when they are connected soma to soma, but seemingly not when they are connected via extensions (Grønlien et al., 2019). Whether or not these long-range connections permit intercellular communication and thus synchronized secretion is presently unknown.

Cellular extensions toward blood vessels have also been seen in the fish pituitary. In juvenile zebrafish, some Fsh-producing gonadotropes were found to project long cellular extensions toward blood vessels (Golan et al., 2015). Similar extensions have been documented in the medaka pituitary, projecting from Lh gonadotropes toward blood vessels (Fontaine and Weltzien, 2019; Grønlien et al., 2019). Within these extensions, Lh protein is abundant all the way to the extremities, indicating that active release sites may be located at the end of the extensions. However, whether these extensions are plastic, and thus their abundance changes according to the physiological stage of the fish, remains to be investigated.

4.5. Summary

In this chapter, we have shown that in mammals, most pituitary cell types connect with other cells in complex networks, introducing a potential mechanism for very efficient secretion control that has been shown to be subject to plasticity when large changes in secretion are needed. In fish, such networks also exist, but have been far less studied.

Although it is well established in many fish species that most of the adenohypophyseal endocrine cells are more or less clustered in specific areas, and functional networks are evident for some cell types, how this clustering takes place is largely unknown. Is the clustering process triggered by hypothalamic (like Gnrh) or peripheral (like sex steroids) signals like indicated in mammals (Navratil et al., 2007; Sanchez-Cardenas et al., 2010)? Are heterotypic networks more common than presently known?

Functionally, there is no doubt that the different endocrine axes extensively interact, but most of the heterotypic communication within the pituitary described to date is via paracrine signaling. Indeed, much less is known about potential interactions via physical links through extensions or soma to soma connections. Whether synchronization of hormone release from the adenohypophysis is mediated by extensive gap junctional communication or other mechanisms remains an open question.

Although cellular extensions have been described for several pituitary cell types in several different fish species, few studies have tried to assess the nature and potential roles of these extensions (Fig. 5B and C). In fact, in many of the references cited above, the extensions or processes are only mentioned briefly. We have experienced that the delicate cellular extensions are easily destroyed by the elaborate procedures necessary for many microscope preparations, and thus are difficult to study. It is likely that the increasing use of endogenous fluorescence markers for pituitary cell types, allowing microscopy of living cells and tissues, will lead to more descriptions and analyses of cellular extensions and networks in the teleost field. The many observations of cellular extensions raise several important questions. Do the extensions form homotypic (or heterotypic) cellular networks? Do they extend to blood vessels, permitting easy exchange of hormones? Are they plastic structures, modified during development or to adapt to new situations, and static during stable periods? How do these structures differ between mammals and fish, and between different fish

Table 1

	Mammals	Fish
Plasticity at the cellular level		
Regulation of Gnrh receptors (Gnrhr): Sensitivity to ligands	- 1–2 GnRHR isoforms. - Levels varies during maturation with a daily rhythm during estrous. - Social interactions affect LH secretion, but role of GnRHR in process is not known. - Effects of GnRH (+/−) and sex steroids (+/−) on *Gnrhr* levels.	- Up to 6 isoforms of Gnrhr. Some may have specialized functions. - Levels varies during maturation with a daily rhythm during sexual maturation. - Social interactions affect *gnrhr* expression levels. - Effects of Gnrh (+/−) and sex steroids (+/−) on *gnrhr* levels in some species.
Regulation of cytosolic Ca^{2+} levels in gonadotropes	- IP3R essential to mobilize Ca^{2+} from internal stores. - The role of RyR in mobilizing Ca^{2+} from internal stores is not clear. - Electrically excitable and rely on Ca^{2+}, K^+, and Na^+ channels and ion exchangers to regulate firing and thereby $[Ca^{2+}]_i$. - Several signals including estrogens influence channel composition.	- IP3R essential to mobilize Ca^{2+} from internal stores. - RyR may also function in Ca^{2+} mobilization in some species. - Electrically excitable and rely on the same groups of ion channels as mammalian gonadotropes to control $[Ca^{2+}]_i$. - Regulation of channel composition is not understood but varies with the reproductive state
Plasticity at the population level		
Presence and differentiation of pituitary progenitor cells	- Sox2 + progenitor cells have been observed lining the pituitary cleft and their pluripotency has been demonstrated. - Progenitor cells appear important for proliferation of some endocrine cell populations, but role unclear for gonadotropes.	- Sox2 + cells have been observed at the neurohypophyseal-adenohypophyseal junction, but their pluripotency is not confirmed. - Their role and importance in the proliferation of endocrine cells remain unknown.
Proliferation of gonadotropes	- Shown to play important role (e.g. after castration).	- Has been demonstrated *in vivo* but the role is not clear.
Phenotypic conversion (transdifferentiation)	- Transdifferentiation of other endocrine cells into gonadotropes or the reverse has been observed *in vitro* and in adenomas. - Phenotypic change from mono-hormonal to bi-hormonal gonadotropes or the reverse have been described *in vivo*	- Transdifferentiation from other cell types has been suggested but never demonstrated. - Phenotypic change of gonadotropes from Fsh to Lh or bi-hormonal phenotype has been observed *in vitro*.
Regulation of gonadotrope proliferation	- GnRH control proliferation and phenotypic determination. - Steroids suppress proliferation. - Paracrine factors control the phenotypic determination.	- Gnrh control phenotypic determination but the direct effect on proliferation is not clear. - Steroids seem to stimulate proliferation. - Paracrine factors seem to participate in the phenotypic determination.
Plasticity at the structural level		
Gonadotrope networks	- Formation of homotypic and heterotypic networks observed. - Use mostly soma to soma connections but also cellular extensions to form networks.	- Formation of homotypic and heterotypic networks observed in a few species. - Seem to use soma to soma connections to form networks but very little is known.
Formation of networks through clustering	- Clustering of gonadotropes observed after puberty but role of the cellular extensions in the clustering is not known. - GnRH induces an increased number of cellular extensions.	- Gonadotropes are clustered at all stages and cellular extensions may be used to cluster and connect. - Gnrh induces an increased number of cellular extensions.
Gonadotrope networks facilitate hormone secretion	- Blocking such networks reduces LH release. - Extensions project to blood vessels.	- Blocking such networks reduces Lh release. - Extensions project to blood vessels.

species?

5. Conclusions

As we have described in this review, the adenohypophysis is a highly plastic tissue, able to change significantly over time in order to adjust hormone production and secretion over the life of an animal. We have focused this review on the gonadotropes and described three different levels of plasticity that allow organisms to scale gonadotropin production and release according to need: the plasticity at the cellular level, at the population level, and at the structural level. We have also compared these mechanisms in fish and mammals, as summarized in Table 1.

At the cellular level, we have seen that both hormone synthesis and secretion can be modulated in short time frames, in mammals and fishes. This is partly due to the inputs received by the pituitary cells. Indeed, the brain and peripheral endocrine organs integrate information from the external and internal environments and transmit signals to control gonadotrope pituitary cell activity. The cell composition also plays a major role, as many molecular components contribute to the integration of the different signals. Thus, the presence or not, of the different types of molecules with different properties, and the number of each component will influence the response of the cell. The composition of the cell membrane in terms of ion channels is also important, as the intracellular calcium dynamics and thus hormone release depends on the types of channels available, their number and their location. Similarly to what we have shown for Gnrhr, changes in the specific receptor isoforms for other types of receptors, their location, and numbers will modulate the sensitivity to the myriad of endocrine and neuronal signals received by the pituitary.

At the population level, we have seen that over a longer time frame important remodeling of the composition of the pituitary, in term of cell types, can occur. This level of plasticity allows significant changes in pituitary hormone secretion to be possible and is often related to important biological events occurring during the life cycle of the animals. Three mechanisms have been described here: the proliferation and differentiation of progenitor cells; the proliferation of the hormone producing cells themselves; and the phenotypic conversion of differentiated pituitary cells (transdifferentiation). While the two first mechanisms lead to hyperplasia, the last mechanism has been found in both mammals and fish to produce cells with a pluri-hormone phenotype. Therefore, the recent studies in fishes also seriously challenge the model “one cell, one hormone” model that is still commonly accepted.

Finally, at the structural level, we have observed that mammalian and teleost gonadotropes, like other adenohyphyseal endocrine cells, are able to construct and remodel heterotypic and homotypic networks thus improving synchronization of the response. To establish these networks, pituitary cells are able to migrate, possibly aided by cellular

extensions. These extensions can also be used to connect to the blood vasculature, hence allowing a more efficient delivery of the hormones.

We have seen that although these three levels have different effects on the pituitary cells and the pituitary itself, the factors that influence all three mechanisms are often similar. Indeed, inputs from the brain- primarily preoptic-hypothalamic factors- as well as the peripheral endocrine organs and neighboring pituitary cells- have been found to play roles in these three mechanisms.

We have also seen evidence of both evolutionary ancestry and divergence as we compare the plasticity between mammals and the fishes, and when we look within each lineage. For example, the commonalities of hypothalamic-POA signals mediating dramatic changes in gonadotropin cell function, and the ability of the gonadotropes to change their responsiveness to these signals, point to conservation over a long evolutionary history. Some differences, such as the complexity of the Gnrh receptors in fishes are attributable to genome duplication. Other differences, both between mammalian and fish lineages and within each lineage, may be due to natural selection.

We have also seen throughout this review that while significant gains in understanding pituitary plasticity in mammals have been made throughout the years, the knowledge of these phenomena in fish is still limited. This disparity is largely because fewer research teams have focused their efforts on pituitary plasticity in fish, but also due to the historical lack of tools to suitably investigate the related questions. However, many powerful tools have been recently developed and can be applied to these questions in fish. Thus, we hope that more researchers will expand these efforts in the near future to fill the gaps in our understanding of pituitary plasticity.

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Conflicts of interest

The authors declare no conflicts of interest

Disclosure statement

The authors have nothing to disclose.

Nomenclature

We use the following nomenclature: “LH” for protein names in mammals and “Lh” for protein names in fish, “*Lhb*” for gene expression in mammals and “*lhb*” for gene expression in fish. When the phylogenetic group is not specified, we used the fish nomenclature.

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