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Publication date
2021

Link to publication

Citation for published version (APA):
Angelopoulou, E. (2021). *Daily-, estral- and age-dependent regulation of RFRP-3 neurons and their role in luteinizing hormone secretion in female mice*. [Thesis, fully internal, Universiteit van Amsterdam, Université de Strasbourg].

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Chapter 1

General Introduction

Based on:

Angelopoulou, E., Quignon, C., Kriegsfeld, L.J., Simonneaux, V., 2019. Functional Implications of RFRP-3 in the Central Control of Daily and Seasonal Rhythms in Reproduction. Front Endocrinol (Lausanne) 10. https://doi.org/10.3389/fendo.2019.00183

Simonneaux, V., Bahougne, T., **Angelopoulou, E.**, 2017. Daily rhythms count for female fertility. Best Pract. Res. Clin. Endocrinol. Metab. 31, 505–519. https://doi.org/10.1016/j.beem.2017.10.012

GENERAL INTRODUCTION

Adaptation of reproductive activity to environmental changes is essential for breeding success and offspring survival. In mammals, the reproductive system displays regular cycles of activation and inactivation, which are synchronized with seasonal and/or daily rhythms in environmental factors, notably light intensity and duration. Thus, most species adapt their breeding activity along the year to ensure that birth and weaning of the offspring occur at a time when resources are optimal. Additionally, female reproductive activity and the period of full oocyte maturation is highest at the beginning of the active phase, in order to improve breeding success. In reproductive physiology, it is therefore fundamental to delineate how geophysical signals are integrated in the hypothalamo-pituitary-gonadal axis, notably by the neurons expressing gonadotropin releasing hormone (GnRH). Several neurotransmitters have been reported to regulate GnRH neuronal activity, but recently two hypothalamic neuropeptides belonging to the superfamily of (Arg)(Phe)-amide peptides, RFRP-3 and kisspeptin (Kp), have emerged as critical for the integration of environmental cues within the reproductive axis. The goal of this thesis is to explore the temporal regulation of RFRP-3, and consider how it might combine with Kp to improve the synchronization of reproduction at different stages of the adult life.

1. Circadian rhythms are driven by the Suprachiasmatic nucleus

The rotation of the earth around its axis exposes all living organisms to 24-hour light-dark and temperature cycles. Through the course of evolution, most organisms; from bacteria to mammals; developed internal timekeeping systems in order to anticipate predictable daily changes in the environment. Thus, even in the absence of external cues (constant conditions of light, temperature, food, etc.) organisms exhibit behavioral and physiological cycles with a period close to, but usually not exactly 24 hours. In mammals, these cycles are driven by molecular oscillators in the suprachiasmatic nucleus (SCN) of the hypothalamus, the primary circadian pacemaker (Bollinger and Schibler, 2014). The SCN receives photic information from intrinsically photoreceptive retinal ganglion cells (ipRGCs) in the eyes,

which convert electrical signals into chemical ones, through the retinal hypothalamic tract in order to reset its molecular oscillators and synchronize the endogenous circadian clocks with the environment (Bollinger and Schibler, 2014; Hattar et al., 2002).

A plethora of studies established the SCN as the seat of the master clock. While SCN lesions render animals arrhythmic (Moore and Eichler, 1972; Stephan and Zucker, 1972), transplantation of fetal SCN can restore circadian rhythmicity (Ralph et al., 1990; Sawaki et al., 1984; Sollars et al., 1995; Sujino et al., 2003). Clock gene expression, firing activity, intracellular calcium concentration ([Ca2+]i) and glucose consumption change rhythmically in the SCN according to time of day (Green and Gillette, 1982; Inouye and Kawamura, 1979; Noguchi et al., 2017; Schwartz and Gainer, 1977). Dispersed SCN neurons maintain cell autonomous circadian rhythms of clock gene expression and $[Ca^{2+}]i$ levels, even though these rhythms are stronger in intact SCN slices (Noguchi et al., 2017). Importantly, SCN tissue in organotypic cultures can maintain structural coherence and circadian rhythms in gene expression and neuronal activity for months (Brancaccio et al., 2014; Patton et al., 2016; Yamaguchi et al., 2003).

A network of self-sustaining transcriptional and translational feedback loops (TTFLs) underlies the operating molecular mechanism for circadian oscillation within the SCN neurons (Figure 1). At circadian time 0 (CT0), corresponding to dawn, the positive regulators of the loop, CLOCK and BMAL1 form heterodimers that drive the transcription of the clock genes encoding the Period proteins; PER1 and PER2; and the Cryptochrome proteins; CRY1 and CRY2; via enhancer box (E-box) regulatory sequences. PER-CRY proteins form complexes that accumulate in the cytoplasm and enter the nucleus when they reach a threshold to attenuate transcriptional activity, at the end of the circadian day (CT12). During the circadian night (CT12-CT24), *Per* and *Cry* mRNA levels decrease and PER-CRY complexes degrade, therefore allowing the transcriptional cycle to reinitiate itself again after approximately 24 hours. The CLOCK-BMAL1 dimer also drives a complementary feedback loop that involves the transcription of nuclear receptor genes encoding REV-ERBα and REV-ERBβ, which suppress, and RORα and RORβ, which activate the *CLOCK* and *BMAL1* transcription (Hastings et al., 2018). Through the intertwined TTFLs of clock genes, the SCN

can generate robust circadian rhythms and achieve precise circadian timing. Brain regions outside the SCN and peripheral organs also contain such autonomous circadian oscillators, however, they lack strong intercellular coupling and direct signaling from the retina, so they depend on the SCN output in order to sustain circadian rhythmicity and entrain to the day/night cycle (Abe et al., 2002; Amir et al., 2004; Granados-Fuentes et al., 2004).

The circadian oscillation of clock genes in the SCN has been associated with circadian changes in SCN firing activity and neuropeptide synthesis. Multiple studies have demonstrated that the firing rate of SCN neurons increases during daytime and decrease at night, both in nocturnal and diurnal rodents, even under constant darkness (Green and Gillette, 1982; Inouye and Kawamura, 1979; Meijer et al., 1998; Sato and Kawamura, 1984; Welsh et al., 1995). Alterations in the molecular clock components change the circadian rhythms in behavior and in the SCN electrical activity, by changing clock gene-dependent molecular feedback loops (Liu et al., 1997; Meng et al., 2008) and clock gene deficient mice that are arrhythmic, lack circadian oscillations in the SCN firing activity (Albus et al., 2002). Altogether, these findings suggest that an intact molecular clock is necessary for the generation of circadian rhythms in the SCN electrical activity.

The vast majority of SCN neurons are GABAergic and co-express one or more neuropeptides (Buijs et al., 1995; Romijn et al., 1997). Based on anatomical connections and peptide expression, the SCN can be divided in two subregions: the core, receiving direct input from the retinal ipRGCs and mainly expressing vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP); and the shell, receiving input from limbic, hypothalamic and brainstem nuclei, and mainly expressing arginine vasopressin (AVP) (Abrahamson and Moore, 2001). VIP mRNA and protein expression display daily variations in the SCN, peaking during the middle of the dark period and decreasing during the light period (Dardente et al., 2004; Shinohara et al., 1999, 1993). Similarly, AVP mRNA and peptide release in the SCN exhibit daily variations, peaking around the middle of the light period and decreasing during the dark period (Dardente et al., 2004; Kalsbeek et al., 1995). Within the SCN, VIP acts primarily on VPAC2 receptors, the expression of which peaks during the subjective morning

(An et al., 2012), while AVP acts primarily on V1a receptors, the expression of which peaks during the dark period (Li et al., 2009).

The output of the SCN is organized in three major pathways: 1) one pathway runs dorsally and rostrally into the medial preoptic area (POA) and continues into the paraventricular nucleus of the thalamus, 2) a second pathway runs caudally to the retrochiasmatic area and the capsule of the ventromedial nucleus, 3) a third pathway that travels in an arc dorsally and caudally, giving off terminals along the course through the regions above the SCN such as the subparaventricular area and the paraventricular hypothalamic nucleus (PVN). A small part of these fibers continues dorsocaudally into the dorsomedial nucleus of the hypothalamus (DMH) where they terminate along its length (Saper et al., 2005). Via these output pathways the SCN drives numerous behavioral and physiological functions, among which is the reproductive activity (Williams and Kriegsfeld, 2012).

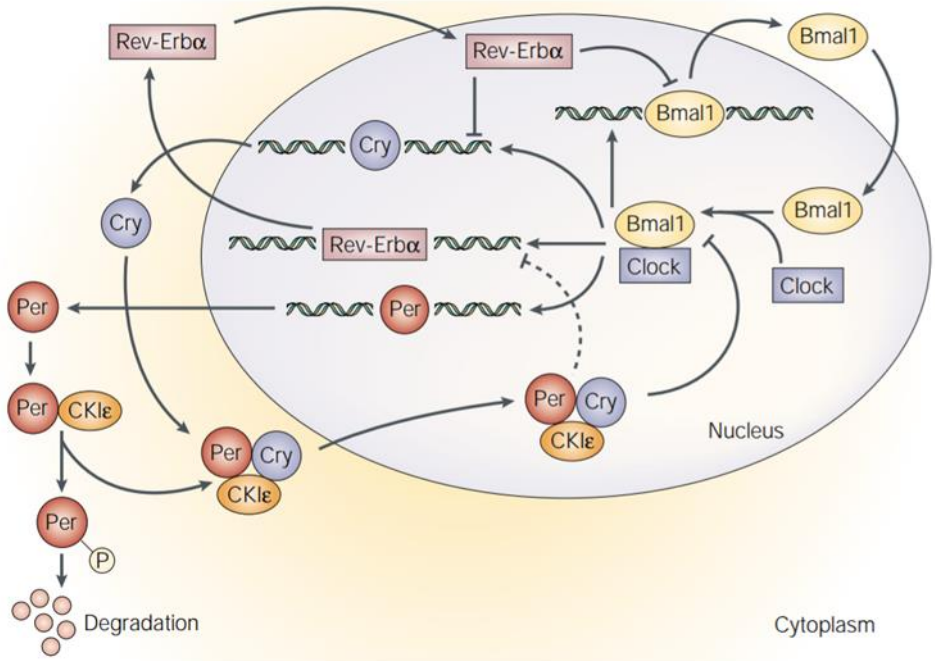

Figure 1: *Schematic representation of the molecular clock mechanism in SCN neurons. Transcriptional factors Clock and Bmal1 form heterodimers and bind to E-box sequences in the promoters of the Cry, Per and Rev–Erbα genes to activate transcription at the beginning of the circadian day. The Clock-Bmal1 heterodimer can also inhibit Bmal1 transcription. After transcription and translation, the Rev–Erbα protein enters the nucleus to suppress the transcription of Bmal1 and Cry genes. While Per proteins accumulate in the cytoplasm, they become phosphorylated (P) by casein kinase I ε (CKIε) and then degraded by ubiquitylation. Late in the subjective day, however, Cry accumulates in the cytoplasm, promoting the formation of CKIε/Per/Cry complexes, which enter the nucleus at the beginning of the subjective night. Once in the nucleus, Cry disrupts the Clock/Bmal1 transcriptional complex, resulting in the inhibition of Cry, Per and Rev–Erbα transcription, and the stimulation of Bmal1 transcription. The interacting positive and negative feedback loops of circadian genes ensure low levels of Per and Cry, and a high level of Bmal1 at the beginning of the new circadian day. Solid lines indicate direct regulation, and dashed lines indicate indirect regulation. Image from Fu and Lee (2003).*

2. Role of RFRP-3 in the central control of female reproduction

2.1 Functional organization of the Hypothalamo-Pituitary-Ovarian (HPO) axis

Mammalian reproduction is tightly controlled by a small set of neurons producing the neuropeptide GnRH. The GnRH cell bodies are concentrated in specific hypothalamic areas [the preoptic area, the vascular organ of the lamina terminalis and, in non-rodent species, the mediobasal hypothalamus] and project principally to the median eminence where they release GnRH in a pulsatile manner in the portal blood supply of the anterior pituitary (Marques et al., 2000). Within the anterior pituitary GnRH stimulates the secretion of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH are released from the anterior pituitary into the general circulation to regulate gonadal gameto- and steroidogenesis respectively (Figure 2).

Mechanisms regulating the activity of GnRH neurons are thought to involve different upstream neuronal inputs. Glutamate and γ-aminobutyric acid fibers, located close to GnRH perikarya and axons, have been shown to stimulate and/or inhibit GnRH release (Morello et al., 1992; Ottem et al., 2002; Piet et al., 2018). Neuropeptide Y-containing fibers also contact a majority of GnRH neurons and predominantly exert an inhibitory effect on GnRH release (Klenke et al., 2010; Roa and Herbison, 2012). Recent studies, however, have highlighted an important role of two other hypothalamic neuropeptides, kisspeptin and RFRP-3, in the regulation of GnRH neuronal activity. Kisspeptin expressing neurons are located in two hypothalamic areas: the preoptic area, where they project to GnRH cell bodies to drive the GnRH surge in female mammals, and in the arcuate nucleus, where they project principally to GnRH fiber terminals in the median eminence to drive pulsatile GnRH release (Pinilla et al., 2012). RFRP-3 expressing neurons are mostly located in the DMH and project to various neuronal populations including GnRH and kisspeptin neurons, yet the effects of RFRP-3 on reproduction seem to vary according to species, sex, and environmental conditions (Henningsen et al., 2016a; Kriegsfeld et al., 2018; Leon and Tena-Sempere, 2015).

To maintain the reproductive axis within proper functioning limits, sex steroids produced by the gonads feed back to the pituitary and hypothalamus. In males, testosterone acts to suppress GnRH and the gonadotropins through negative feedback, whereas in females the feedback is more complex with estradiol (E2) having either positive or negative feedback effects depending on the stage of the ovarian cycle and its circulating concentration. Specifically, during the follicular phase of the ovulatory cycle, low concentrations of E2 exert negative feedback, whereas upon oocyte maturation, higher concentrations of E2 exert positive feedback, triggering a large release of GnRH in the anterior pituitary portal blood supply which, in turn, induces a surge of LH that initiates ovulation (Christian and Moenter, 2010). Contrary to early expectations, GnRH neurons do not appear to be directly responsive to E2 feedback as these cells do not express E2 receptors (ER)α and only express low levels of ERβ (Christian and Moenter, 2010; Leon and Tena-Sempere, 2015). Likewise, mice with a GnRH neuron-specific deletion of ERβ do not exhibit any gross reproductive dysfunction (Cheong et al., 2014). Therefore, the central structures integrating sex steroid feedback have to be upstream of GnRH neurons and evidence now indicates that kisspeptin neurons and, to a less and unclear extent, RFRP-3 neurons are relaying gonadal hormone feedback to the reproductive system (Kriegsfeld et al., 2006; Poling et al., 2012; Smith et al., 2005a, 2005b; Tumurbaatar et al., 2018).

Because reproduction is particularly energetically demanding, it is critical that intrinsic and extrinsic factors contribute to optimizing breeding success and offspring survival as much as possible. Therefore, the reproductive axis is sensitive to various signals such as metabolic activity, stress level, development stage, hormonal milieu, and geophysical cues. Thus, in female mammals, timing of the preovulatory LH surge is driven by daily signals in addition to positive E2 feedback. Additionally, in seasonal breeders, annual changes in daily light duration (photoperiod) synchronize reproduction with the time of the year (Henningsen et al., 2016a). Recent studies have highlighted the pivotal role of RFRP-3 neurons, as well as kisspeptin neurons, in relaying both daily and seasonal cues to the HPG axis, particularly to GnRH neurons.

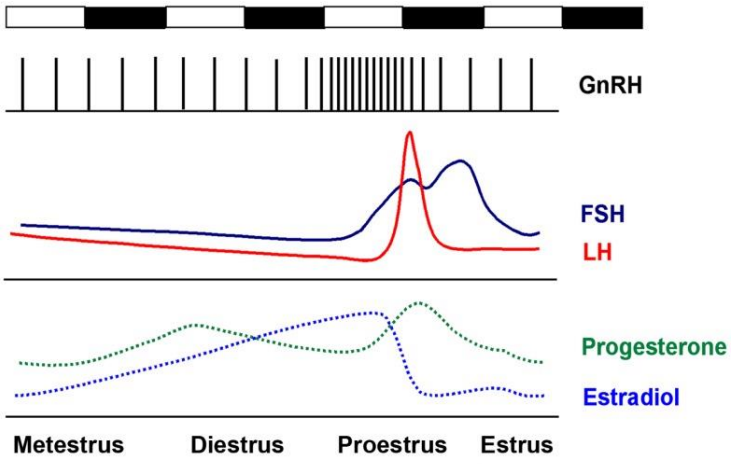

Figure 2: *Rhythmic hormone secretion during the rodent estrous cycle. In mice, ovulation occurs every 4–5 days. Metestrus and diestrus are characterized by low, but slowly increasing levels of estradiol. During the late afternoon of proestrus, elevated estradiol levels induce a burst of GnRH release from the hypothalamus, which triggers the preovulatory LH surge at approximately the start of the active (dark) period. Image from (Miller and Takahashi, 2014).*

2.2 The RFRP-3 system

The ortholog of RFRP-3 was originally discovered in birds, with Tsutsui et al. identifying a novel (Arg)(Phe) hypothalamic peptide that inhibited pituitary gonadotropin secretion from cultured quail pituitary (Tsutsui et al., 2000). Because this peptide selectively inhibited the gonadotropins, without altering other pituitary hormones, the authors named it gonadotropin-inhibitory hormone (GnIH). Subsequent findings indicated the GnIH receptor to be expressed in quail pituitary (Ubuka et al., 2012; Yin et al., 2005) and that *in vivo* GnIH administration decreases common α, LHβ, and FSHβ subunit expression (Ubuka et al., 2006; Yin et al., 2005). In birds, the GnIH precursor cDNA encodes one GnIH and two GnIH-related peptides (GnIH-RP1 and GnIH-RP2) (Molnár et al., 2011; Tsutsui et al., 2000). In mammals, the homologous gene encodes three peptides [RFamide-related peptides (RFRP)], with RFRP-1 and −3 both being RFamide peptides, while RFRP-2 is not (Tsutsui and Osugi, 2009). Since the initial discovery of these RFamide-related peptides in mammals, most findings in

reproductive biology have focused on RFRP-3 as the mammalian ortholog of GnIH. As described further below, studies across different mammalian species indicate a pronounced role for this neuropeptide in regulating reproductive function.

The receptor for GnIH/RFRP-3 is a G-protein coupled receptor (GPR), originally named OT7T022 (Hinuma et al., 2000), but now more commonly referred to by the name of the receptor for which it was found to be identical, the formerly-orphaned GPR147. Around the same time as this discovery, two receptors for another RFamide-peptide, neuropeptide FF, were identified and called NPFFR1 and NPFFR2 (Bonini et al., 2000). NPFFR1 was found to be identical to GPR147, whereas NPFFR2 was identical to another GPR, GPR74. GPR147 has a high affinity for GnIH/RFRP-3, whereas NPFF exhibits potent agonistic activity at GPR74 (Bonini et al., 2000; Liu et al., 2001; Yin et al., 2005; Yoshida et al., 2003). Together, these findings revealed GPR147/NPFFR1 as the GnIH/RFRP-3 receptor. GPR147 most-commonly couples to an inhibitory G protein (Gαi), with GnIH/RFRP-3 suppressing cAMP activity (Hinuma et al., 2000; Shimizu and Bédécarrats, 2010). However, in some instances, GPR147 is coupled to Gαs or Gαq proteins (Gouardères et al., 2007) and this differential coupling may account for the reported disparity in the effects of RFRP-3.

As indicated above, in most rodents, RFRP-3 perikarya are restricted to the DMH (Henningsen et al., 2016a; Kriegsfeld et al., 2018; Tsutsui and Ubuka, 2018), although, in rats, a significant number of cells are also observed in the region between the DMH and the ventromedial nucleus of the hypothalamus (VMH) (Hinuma et al., 2000; Legagneux et al., 2009) (Figure 3). In mammals, RFRP-3-immunoreactive (-ir) fiber projections are extensively scattered throughout the diencephalon, mesencephalon and limbic structures (Henningsen et al., 2016b; Kriegsfeld et al., 2006; Smith et al., 2008; Yano et al., 2003), providing divergent neural pathways to broadly influence neurophysiology and behavior.

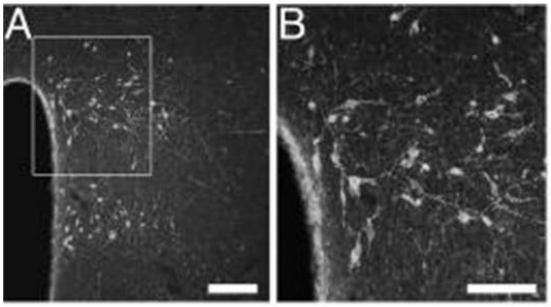

Figure 3: *GnIH/RFRP-3 cell bodies are tightly clustered in the dorsal and ventral regions of the DMH in Syrian hamsters (Scale bar: 200 µm). The box in the top image outlines the cells bodies shown at high power. Image from (Kriegsfeld et al., 2006).*

2.3 Evidence for a role of RFRP-3 in the central control reproduction

RFRP-3 acts both directly and indirectly to influence GnRH cell function. For example, RFRP-3 cell fibers form close contacts with GnRH cells (Figure 4) and about a third of GnRH cells express GPR147, pointing to direct actions of RFRP-3 on the GnRH system (Rizwan et al., 2012; Ubuka et al., 2012, 2009a, 2009b). Likewise, RFRP-3 inhibits cellular activity in about 40% of GnRH cells *in vitro* (Ducret et al., 2009; Wu et al., 2009). RFRP-3 may also act to suppress GnRH cellular activity via kisspeptin cells, as RFRP-3 cell projections form close connections with kisspeptin neurons in mice, sheep and monkeys (Poling et al., 2013; Qi et al., 2009; Ubuka et al., 2009a), with a small percentage of kisspeptin cells in the anteroventral periventricular nucleus (AVPV) and ~25% of kisspeptin cells in the arcuate nucleus, expressing GPR147 in mice (Poling et al., 2013; Rizwan et al., 2012).

Generally, RFRP-3 inhibits gonadotrophin synthesis and/or secretion across mammals, including humans (Clarke et al., 2008; George et al., 2017; Henningsen et al., 2017; Johnson et al., 2007; Kriegsfeld et al., 2006; Tsutsui and Ubuka, 2018). In some cases, however, RFRP-3 stimulates gonadotropin secretion, with differences observed based on sex, season or reproductive status (Table 1) (Figure 5 and 6). For example, in male Syrian hamsters (*Mesocricetus auratus*), RFRP-3 increases GnRH neuronal activity (i.e., increases *c-Fos* expression) and increases gonadotropin and testosterone release (Ancel et al., 2012). This

pattern differs from that observed in female Syrian hamsters, where RFRP-3 suppresses LH if administered around the time of the LH surge (Henningsen et al., 2017; Kriegsfeld et al., 2006). Similarly, in male mice (*Mus musculus*), RFRP-3 stimulates LH secretion, at least in part via actions on kisspeptin as the stimulatory effect of RFRP-3 is diminished in kisspeptin receptor knockout mice (Ancel et al., 2017). In female mice, as in Syrian hamsters, RFRP-3 inhibits LH when estradiol concentrations are high around the time of the LH surge, but is without effect during diestrus or in ovariectomized females with low estradiol concentrations when provided exogenously (Ancel et al., 2017). Finally, in male Siberian hamsters (*Phodopus sungorus*), RFRP-3 stimulates LH secretion in short-day, reproductively-inhibited hamsters, but inhibits LH secretion in long-day, reproductively-competent animals (Ubuka et al., 2012). Together, these findings confirm a role of RFRP-3 in the central control of reproduction, but its effects are dependent on species, sex, reproductive status and hormone concentrations, most likely due to the specific G-protein to which GPR147 is coupled. Surprisingly, however, GPR147/NPFFR1 female null mice exhibit moderate reproductive phenotypes with larger litter, and increased arcuate kisspeptin synthesis, higher serum FSH concentrations, and augmented LH responses to GnRH (León et al., 2014). The disparate results in the effects of GPR147/NPFFR1 inactivation and exogenous administration of RFRP-3 probably are explained by compensatory mechanisms by other RF-amide systems.

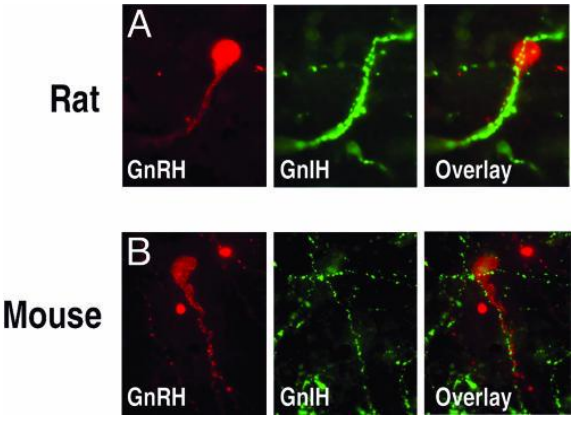

Figure 4: *GnIH fibers contact GnRH neurons in rats and mice. Images are shown as GnRH (red) alone and GnIH fibers (green) alone, followed by their respective overlays, taken at ×1,000 at the light level. Image from Kriegsfeld et al. (2006).*

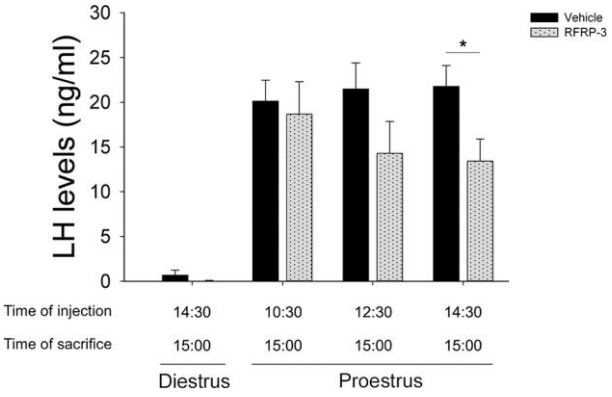

Figure 5: *Effects of intracerebroventricular RFRP-3 administration at different times of the day and estrous stages in long day-adapted female Syrian hamsters. In female hamsters, an injection of vehicle (4 µL Ringer's solution) or RFRP-3 (1500 ng in 4 µL Ringer's solution) was given in diestrus (14:30), as well as at 3 different time points on the day of proestrus (morning, 10:30; midday, 12:30; and just before the surge in LH, 14:30). Circulating LH was measured at 15:00 in diestrus and proestrus (time of the putative LH surge); data represent the mean level of LH ± standard error of mean (n = 7 in proestrus, n = 6 in diestrus); *P < 0.05 indicates a statistically significant effect of RFRP-3 when compared with vehicle. Image from (Henningsen et al., 2017).*

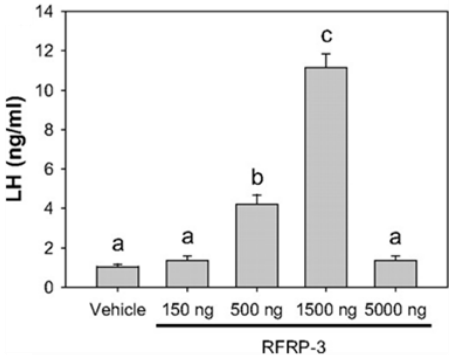

Figure 6: *Intracerebroventricular injection of RFRP-3 stimulates LH secretion in the male Syrian hamster. Centrally administered hamster RFRP-3 (150–5000 ng, icv) dose dependently increased LH secretion after 30 min. Data represent the mean ± SEM (n = 6/group). Bars with differing letters differ significantly (P < 0.05 by one way ANOVA followed by Tukey's analysis). Image from (Ancel et al., 2012).*

Table 1: Overview of the in vivo and in vitro effects of RFRP-3 on gonadotropin secretion in different species.

In vivo:

Species	Sex and status	Effect of GnIH/RFRP-3 administration	Reference
Human	Female - post-menopause	iv infusion: Inhibits LH secretion	(George et al., 2017)
Mouse	Female - Proestrus Female - Diestrus Female - OVX Female - OVX+E2	icv administration: Inhibits LH secretion No effect Inhibits LH secretion No effect	(Ancel et al., 2017)
Mouse	Male - intact/CAST	icv administration: Stimulates LH secretion	(Ancel et al., 2017)
Rat	Female - intact/OVX	icv and ip administration: Inhibits LH secretion	(Kriegsfeld et al., 2006; Pineda et al., 2010)
Rat	Male - intact/CAST	icv and ip administration: Inhibits LH secretion	(Johnson et al., 2007; Pineda et al., 2010)
Syrian Hamster	Female - OVX	icv and ip administration: Inhibits LH secretion	(Henningsen et al., 2017; Kriegsfeld et al., 2006)
Syrian Hamster	Male	icv administration: Stimulates LH secretion	(Ancel et al., 2012)
Siberian hamster	Male in LP Male in SP	icv administration: Inhibits LH secretion Stimulates LH secretion	(Ubuka et al., 2012)
Sheep	Female - OVX	iv administration: Inhibits LH secretion or no effect	(Clarke et al., 2008) (Decourt et al., 2016)
Goldfish		ip administration: Inhibits LH secretion	(Zhang et al., 2010)

In vitro:

Species	Culture	Effect of incubation with GnIH/RFRP-3	Reference
Bird	Quail anterior pituitary	Inhibits LH and FSH secretion	(Tsutsui et al., 2000)
Cow	Bovine anterior pituitary cells	Suppresses LH secretion	(Kadokawa et al., 2009)
Sheep (OVX)	Ovine pituitary cells	Inhibits LH and FSH secretion	(Clarke et al., 2008; Sari et al., 2009)

2.4 Evidence for a role of RFRP-3 in seasonal rhythms of reproduction

The marked changes in environmental factors throughout the year require species to display adaptation of their behavior and physiology to these predictive seasonal changes in order to survive. Notably, many mammalian species synchronize their reproductive activity with one particular time of the year so that depending on the duration of female gestation, offspring are born at the most favorable period of the year, usually in spring when temperature, humidity and food availability are optimal (Bronson, 1988). Thus, two categories of breeders are described depending on the mating period: long-day (LD) breeders like rodents with a few weeks of gestation and short-day (SD) breeders like sheep, goats, or deer, with a few month of gestation (Goldman, 2001).

Since the 60's, it has been known that the pineal hormone melatonin is a major signal for the synchronization of reproduction with the seasons. Indeed, melatonin synthesis and release occurs only during the night and, therefore, the nocturnal production of melatonin is longer in the short days (SD) in autumn/winter as compared to long days (LD) in spring/summer (Hastings et al., 1985). Hoffman and Reiter were the first to demonstrate that the elimination of this neuroendocrine calendar by pinealectomy abolishes the reproductive response of Syrian hamsters to the photoperiod signal (Hoffman and Reiter, 1965). It was later established through timed melatonin infusion experiments that the duration of circulating melatonin, and not its concentration or phase, is the crucial variable triggering photoperiodic adaptations in all seasonal species (Bartness et al., 1993; Goldman,

2001). Intriguingly, although the mechanism is unknown, the same photoperiodic melatonin signal has an opposite reproductive effect on LD and SD breeders.

In early studies, it was shown in seasonal quail and rodents that GnIH and RFRP-3 (Kriegsfeld et al., 2006; Tsutsui et al., 2000), respectively, are synthesized in hypothalamic neurons and are able to alter LH release, altogether indicating that this peptide may be involved in the seasonal regulation of reproduction. The first studies on quail and sparrow reported seasonal variation in GnIH synthesis that correlated with seasonal changes in reproduction (Bentley et al., 2003; Ubuka et al., 2005). Additionally, melatonin administration, in pinealectomized and enucleated (pineal gland and eyes removed to eliminate all sources of melatonin) quail, was shown to act directly on GnIH neurons to inhibit GnIH synthesis in a dose-dependent manner (Ubuka et al., 2006).

Subsequently, it was found that, in seasonal rodents, the number of RFRP-3 neurons in the dorso/ventromedial part of the DMH displayed marked photoperiodic changes (Revel et al., 2008). Indeed RFRP-3 synthesis was higher in LD-adapted, sexually active animals as compared to SD-adapted sexually inactive male Syrian and Siberian hamsters (Mason et al., 2010; Revel et al., 2008). Like in birds, although in an opposite manner, seasonal variation in RFRP-3 synthesis depends on melatonin, since pinealectomy increases and injection of melatonin decreases, the number of RFRP-3 expressing neurons in hamsters (Revel et al., 2008; Ubuka et al., 2012). Additionally, expression of GPR147 in various hypothalamic areas (Henningsen et al., 2016b) and the number of GnRH cell bodies receiving RFRP-3 fiber contacts (Smith et al., 2008; Ubuka et al., 2012) were increased in LD hamsters.

In male LD-adapted Syrian hamsters, an acute injection of RFRP-3 was found to increase LH, FSH and testosterone secretion. Furthermore, a chronic central infusion of RFRP-3 in SD-adapted, sexually inhibited male Syrian hamsters restored gonadal activity to that of hamsters kept in LD conditions (Ancel et al., 2012). Intriguingly, despite an acute inhibitory effect of RFRP-3 on the preovulatory LH surge in LD-adapted female Syrian hamsters, a chronic central infusion in sexually inactive SD-adapted females fully restored reproductive activity, as observed in male hamsters (Henningsen et al., 2017). Even more complexity was revealed following studies in closely-related male Siberian hamsters, where the effect of

RFRP3 on LH secretion depended on photoperiod, with RFRP-3 being stimulatory in SD-adapted and inhibitory in LD-adapted animals (Ubuka et al., 2012). However, administration of different doses of RFRP-3 had no effect on the reproductive status of photo-inhibited Djungarian hamsters of either sex (Cázarez-Márquez et al., 2019). In ewes, initial studies reported RFRP-3 to inhibit gonadotropin secretion (Clarke et al., 2008; Sari et al., 2009). However, a more recent study using different protocols of RFRP-3 administration could not find any effect on LH secretion in ewes (Decourt et al., 2016).

Therefore, although the melatonin-dependent photoperiodic regulation of RFRP-3 neurons is well conserved among seasonal species, the role of RFRP-3 in the seasonal regulation of reproduction is not straightforward and appears to be species dependent. Data so far, however, are insufficient to conclude whether RFRP-3 is responsible for the LD or SD breeding activity in seasonal species.

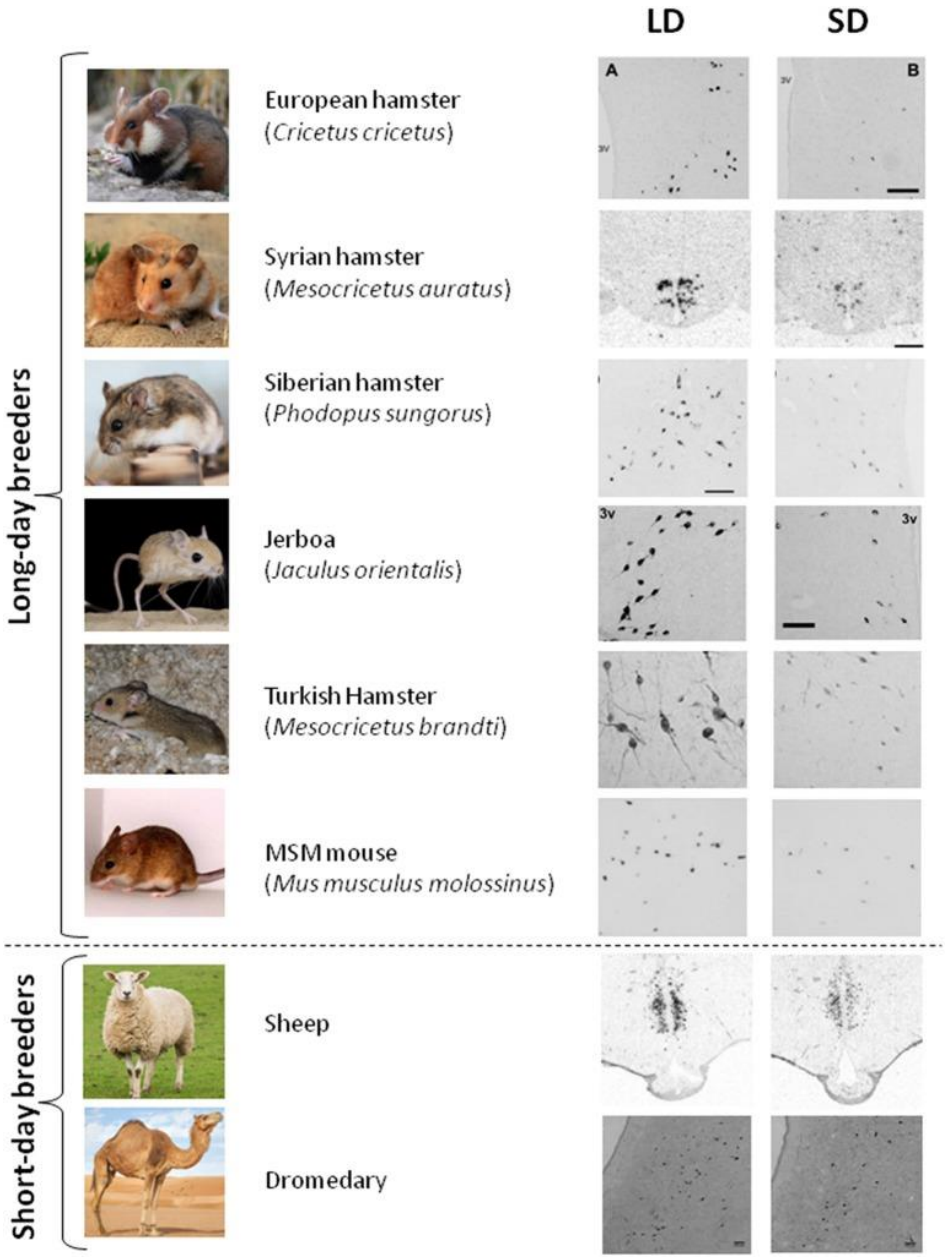

Figure 7: *RFRP-3 synthesis in the medial hypothalamus exhibits a conserved seasonal pattern. RFRP-3 expression, attested by the number of neurons or the level of Rfrp mRNA, is higher in the long-day (LD) condition as compared to the short-day condition (SD). Data are shown for LD breeders (European hamster, Syrian hamster, Siberian hamster, Jerboa, Turkish hasmter, and MSM mouse) as well as for SD breeders (sheep, dromadary). Image from:*

(Angelopoulou et al., 2019) and adapted from (Sáenz de Miera et al., 2014) (European hamster), (Revel et al., 2008) (Syrian hamster), (Talbi et al., 2016a) (Jerboa),(Piekarski et al., 2014) (Turkish hamster), (Miera et al., 2020) (MSM mouse), (Lomet et al., 2018)(sheep), (Ainani et al., 2020) (Dromedary), with appropriate permissions obtained from the copyright holders.

2.5 Potential roles of RFRP-3 in the pituitary and gonads

In addition to its actions on GnRH neurons, RFRP-3 may alter gonadotropin synthesis and secretion also via the pituitary, although findings are disparate across studies and species. For example, RFRP-3 projections have been shown to project to the outer layer of the median eminence [hamsters (Gibson et al., 2008), sheep (Clarke et al., 2008), macaque (Ubuka et al., 2009a), and humans (Ubuka et al., 2009b)]. In contrast, using peripheral injections of fluorogold to label hypophysiotropic cells, RFRP-3 cells were not labeled in rats (Rizwan et al., 2009). In other studies, RFRP-3 terminal fibers in the median eminence are sparse or absent [mice (Ukena and Tsutsui, 2001); brushtail possum (Harbid et al., 2013); macaque (Smith et al., 2010)]. Although results are thus equivocal regarding projections to the median eminence across species, GPR147 is expressed in the pituitary of hamsters (Gibson et al., 2008) and humans (Ubuka et al., 2009b) and RFRP-3 has been shown to inhibit gonadotropin release in cultured pituitaries from sheep (Sari et al., 2009), cattle (Kadokawa et al., 2009), and rat (Pineda et al., 2010). In ewes, RFRP-3 is detected in hypophyseal portal blood and exogenous RFRP-3 has been reported to significantly reduce the GnRH-induced LH response (Smith et al., 2012). In another study, however, peripheral administration of RFRP-3 in ewes was unable to inhibit pulsatile LH secretion or the E2-induced LH surge (Decourt et al., 2016), raising the question of whether or not RFRP-3 acts on pituitary gonadotropes despite being detectable in portal blood.

In addition to potential actions at the level of the pituitary, RFRP-3 also appears to be produced and act locally at other places, to regulate gonadal function. Early work discovered that GnIH is synthesized in ovarian granulosa cells and in the testicular interstitial layer and seminiferous tubules of birds (Bentley et al., 2008). Moreover, in birds, GnIH application decreases testosterone release from gonadotropin-stimulated testes *in*

vitro, pointing to a functional role for gonadal GnIH (McGuire et al., 2011). Later, it was shown that RFRP-3 is synthesized in the gonads of all mammals studied to date (Bentley et al., 2017), including humans (Oishi et al., 2012), non-human primates (McGuire and Bentley, 2010), Syrian hamsters (Zhao et al., 2010), mice (Oishi et al., 2012; Singh et al., 2011), rats (T et al., 2015), ewe (Li et al., 2014), and pigs (Fang et al., 2014). Across species, the gonads synthesize RFRP-3 and GPR147 (Bentley et al., 2017, 2008; McGuire and Bentley, 2010; Oishi et al., 2012; Singh et al., 2011). In mice, testicular RFRP-3 synthesis increases during reproductive senescence, possibly contributing to aging-related decrements in testicular functioning (Anjum et al., 2012). In human granulosa cell cultures, RFRP-3 inhibits gonadotropin-induced intracellular cAMP accumulation and progesterone secretion (Oishi et al., 2012). Finally, RFRP-3 and GPR147 are synthesized in ovarian granulosa cells and antral follicles during proestrus and estrus and in luteal cells during diestrus in mice (Singh et al., 2011), suggesting participation in follicular development and atresia. Together, these findings suggest that GnIH/RFRP-3 is commonly synthesized in the gonads across species and may act locally to fine-tune gonadotropin-regulated gonadal functioning.

2.6 Potential role of RFRP-3 in reproduction through metabolic activity and stress regulation

Although RFRP-3 is consistently reported to regulate reproductive axis function, the effect on GnRH neuronal activity and gonadotropin secretion is highly dependent on species, sex and environmental conditions (Ancel et al., 2017; Henningsen et al., 2016b). Determining the exact mechanism of RFRP-3 action is further complicated by increasing evidence indicating that RFRP-3 is a pleiotropic peptide involved in functions other than reproduction, notably metabolic activity and the stress response (Kriegsfeld et al., 2018; Schneider et al., 2017; Takayanagi and Onaka, 2010). Because reproduction is modulated by energy state and stress conditions, it is possible that RFRP-3, at least in part, indirectly regulates reproduction via metabolic- and stress-regulated mechanisms. Food intake and metabolic activity, for example, display major circadian and seasonal changes in mammals, which may interfere with reproductive cycles. Indeed, metabolic alterations such as food

restriction or obesity are known to impair reproduction. As RFRP-3 increases food intake in various species, possibly through actions on orexigenic NPY neurons (Cázarez-Márquez et al., 2020; Johnson et al., 2007; Talbi et al., 2016b), and food restriction decreases RFRP-3 synthesis in rats and sheep (Li et al., 2014; M et al., 2014), it is possible that RFRP-3 may also impact reproductive activity indirectly via metabolic pathways (Wahab et al., 2015). Likewise, a number of studies report that acute or chronic stress increases RFRP-3 synthesis via increased levels of glucocorticoids (Clarke et al., 2016; Kirby et al., 2009; Yang et al., 2017) and this stress-induced increase in RFRP-3 is associated with an inhibition of LH secretion (Kirby et al., 2009). Finally, *Rfrp* gene silencing completely rescues stress-induced infertility in female rats (Geraghty et al., 2015), strengthening the implication that stress can influence reproductive function via the RFRP system. In summary, although there is much more to learn, findings to date provided clear evidence for a role for RFRP-3 in the daily and seasonal regulation of reproduction. Whether RFRP-3 effectuates its influence through direct actions on the reproductive axis, and/or indirectly via actions on intermediate systems (e.g., stress or metabolic systems), requires further examination. The advent and application of new experimental tools and animal models to more precisely dissect the roles of this neuropeptide will help to further clarify the specific role of RFRP-3 in the LH surge/ovulation and the neural pathways by which melatonin inevitably influences RFRP3 cell activity.

3. RFRP-3 contributes to the daily rhythm of reproduction in female rodents

3.1 Daily and ovarian rhythms in female reproduction

Successful female reproduction requires the activation of specific neuronal and hormonal pathways in order to synchronize ovulation with maximal locomotor activity and an optimal arousal state. Female mammals display rhythms of different, recurrent time scales that range from minutes (pulsatile GnRH release) to hours/days (LH surge), days/weeks (ovarian cycle) or even months (seasonal reproduction).

Ovarian activity displays regular cycles (~28 days in women and 4–5 days in rodents) driven by changes in circulating levels of the pituitary gonadotropins LH and FSH. During the first stage of the ovulatory cycle (follicular phase in humans, metestrus-diestrus in rodents), FSH secretion gradually increases, promoting ovarian follicular development. In turn, maturing follicles secrete increasing concentrations of E2. The second stage of the reproductive cycle (luteal phase in women; proestrus-estrous in rodents) is immediately preceded by a pronounced and transient rise in LH secretion (surge) that initiates the release of mature oocyte(s) from ovarian follicles (Figure 8). The generation of the LH surge requires high circulating levels of E2, indicative of follicle maturation, as well as a daily signal, ensuring that ovulation occurs at the right arousal time to optimize breeding success. Indeed, the LH surge occurs at a specific time of day, corresponding to the end of the inactive phase, thus in late afternoon in nocturnal rodents (e.g., mice, rats, hamsters) and early morning in diurnal species (e.g., Nile grass rat, humans) (Kerdelhué et al., 2002; Simonneaux and Bahougne, 2015).

Exploring the pathways by which the circadian clock synchronizes GnRH neuronal activity and upstream modulatory systems is essential to fully understand the mechanisms of female reproduction. Indeed, circadian disruption has been associated with various abnormalities in fertility and reproduction. Early studies in the 50's demonstrated that chemical blocking of neural clock output alters the LH surge in female rats (Everett and Sawyer, 1950, 1949) and hamsters (Stetson and Watson-Whitmyre, 1977). Furthermore, SCN lesions cause anovulation in female rats, presumably resulting from the loss of diurnal

variation in the sensitivity of the reproductive axis to E2 positive feedback (Brown-Grant and Raisman, 1977) and stimulatory input from the SCN (Palm et al., 1999). Indeed, female mice deficient for the clock gene, *Clock*, exhibit abnormal estrous cycles, do not have a detectable LH surge on the day of proestrus, and generally fail to carry pregnancies to term (Miller et al., 2004). Similarly, women with single-nucleotide polymorphisms in the circadian clock gene *ARNTL* exhibit more miscarriages than those without such mutation (Kovanen et al., 2010).

It appears that the circadian signal is sent to the reproductive system each day, but its impact is masked by low circulating E2. Thus, in female rodents provided with chronic, proestrus-like concentrations of E2, daily LH surges are observed for several consecutive days, revealing the circadian mechanism underlying surge generation (Christian et al., 2005; Legan and Karsch, 1975; Norman et al., 1973) (Figure 5). Altogether, these findings, largely obtained in female rodents, indicate that the timing of the preovulatory LH surge is strictly time-gated by a combination of daily and ovarian signals. Although the daily signal is communicated each day by the SCN to the GnRH/LH pathway, E2 secretion from mature oocytes needs to reach a certain threshold in order to exert positive feedback on the HPG axis and allow the generation of the LH surge.

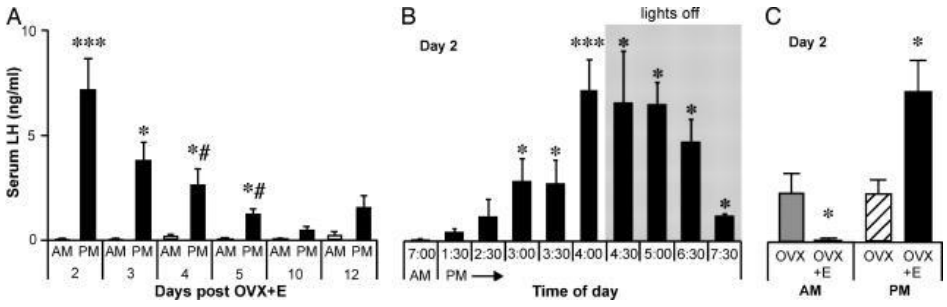

Figure 8: *Induction of daily LH surges by estradiol in mice. (A) Bars represent serum LH concentrations (mean ± SEM) with open bars showing samples obtained at 7 a.m., and filled bars showing samples obtained at 4 p.m., from 2 to 12 days after mice were ovariectomized with an estradiol implant (OVX+E). (B) Serum LH levels (mean ± SEM) sampled in OVX+E mice at various times on day 2 after OVX+E. Gray shading indicates time during which lights were off. LH surge reliably begins ≈1.5 h before lights off (4:30 p.m.). (C) Serum LH levels show no diurnal*

*difference in OVX mice, and estradiol induces negative feedback in the a.m. and positive feedback in the p.m. A, a.m. same-day control; B, 7 a.m. control; C, OVX control. *, P < 0.05; ***, P < 0.001; #, P < 0.01 vs. day 2 p.m. Image from: (Christian et al., 2005).*

3.2 Mechanisms regulating the circadian-estrogen sensitive preovulatory LH surge

Both two principal SCN neurotransmitters, VIP and AVP, are thought to be implicated in relaying daily cues to GnRH neurons and therefore controlling the timing of the preovulatory LH surge. VIP content in the rat SCN displays daily variation, decreasing during the light period and increasing during the dark period. This daily variation is abolished under constant darkness, suggesting that VIP is implicated in the transmission of photic information (Shinohara et al., 1993). Furthermore, the daily rhythm of VIP in the SCN appears sex-dependent since *VIP* mRNA levels peak during the light phase in female rats, but during the dark phase in male rats (Krajnak et al., 1998a). The observation that a central blockade of VIP signaling decreases the LH surge in female rats indicates a role of this peptide in female reproduction (Harney et al., 1996; van der Beek et al., 1999). Indeed, ~45% of the GnRH cells are innervated by VIP-containing fiber terminals and unilateral thermal lesions of the majority of VIP cells in the SCN results in a 50% decrease of VIP nerve contacts on GnRH cell bodies on the lesioned side, compared to the intact side of the brain (van der Beek et al., 1993). Furthermore, the use of anterograde tracing demonstrated a direct connection between the SCN and GnRH neurons (Van der Beek et al., 1997). Interestingly, there is a sex-dependent difference in the VIP-GnRH pathway, with the number of VIP terminals onto GnRH neurons, and the percentage of GnRH neurons contacted by VIP fibers, being higher in females compared to males (Horvath et al., 1998). About 40% of GnRH neurons express the VIP2 receptor (Smith et al., 2000) and exogenous VIP application to brain slices increases GnRH neuron action potential firing and intracellular calcium (Christian and Moenter, 2008; Piet et al., 2016), supporting the idea that VIP may provide a direct excitatory signal from the SCN to the GnRH system.

AVP expression exhibits both daily and circadian variation in the SCN, peaking during the latter part of the light period and dropping during the dark period (Cagampang et al., 1994). AVP release in the SCN vicinity has been found to peak during midday, while minimum release occurs at midnight (Kalsbeek et al., 1995). Unlike VIP, no sex-dependent differences in *AVP* gene expression are found in the SCN (Krajnak et al., 1998a). Increasing evidence indicates that the rhythm in SCN AVP release is critical for the daily timing of the preovulatory LH surge. Indeed, central administration of AVP in OVX, E2-treated rats, bearing complete SCN lesions, is sufficient to trigger a LH surge (Palm et al., 1999). However, the ability of AVP to trigger the surge is time-dependent, with administration during the latter half of the light period, but not the first half, being effective (Palm et al., 2001). Moreover, central administration of a V1a receptor antagonist decreases LH surge amplitude in rats (Funabashi et al., 1999). Finally, in *Clock* mutant female mice, central injections of AVP can restore a preovulatory-like LH surge (Miller et al., 2006). Unlike VIP, SCN AVP neurons appear to regulate the GnRH/LH surge indirectly via kisspeptin neurons located in the preoptic area (AVPV in rodents), a highly sex-dimorphic brain area (Adachi et al., 2007; Smith et al., 2006). Thus, in female rodents, AVPV kisspeptin neurons receive direct SCN-derived AVP inputs and express the V1a receptors (Vida et al., 2010; Williams et al., 2011), and direct application of AVP to brain slices increases neuronal firing and intracellular calcium concentrations in AVPV kisspeptin cells (Piet et al., 2015). Importantly, AVPV kisspeptin neurons display ERα, and E2 not only potently stimulates kisspeptin synthesis (Adachi et al., 2007; Smith et al., 2006, 2005a), but is also required for the AVP-induced activation of kisspeptin cells (Piet et al., 2015). Finally, activation of AVPV kisspeptin neurons coincides with the time of LH surge, during the sleep/wake transition in proestrus or in OVX E2-treated female rodents, but does not display daily rhythms during diestrus or in OVX animals (Chassard et al., 2015; Henningsen et al., 2017; Robertson et al., 2009; Williams et al., 2011).

Therefore, data primarily obtained in female rodents indicate that both SCN-derived VIP fibers acting directly on GnRH neurons, and AVP fibers acting indirectly via preoptic kisspeptin neurons, are involved in the timing of the preovulatory LH surge. In addition to

this mechanism of surge control, RFRP-3 neurons may also be part of the pathway relaying daily time cues from the SCN to GnRH neurons in order to time the preovulatory LH surge, as described further below.

3.3 Evidence for a role of RFRP-3 neurons in the daily timing of the LH surge

The hypothesis for a role of RFRP-3 neurons in the daily timing of the LH surge begins with the observation of a daily rhythm in RFRP-3 neuronal activity, with a lower number of RFRP-3 neurons expressing c-FOS coincident with the timing of the LH surge in female Syrian hamsters (Gibson et al., 2008; Henningsen et al., 2017) and mice (Poling et al., 2017). Equivocal findings are reported regarding the association between the RFRP-3 cell activation state and the number of *Rfrp* expressing neurons, with daily variation in RFRP-3 neuronal activity being associated (Gibson et al., 2008) or not (Henningsen et al., 2017; Poling et al., 2017), with corresponding changes in the number of *Rfrp* expressing cells. In ewes, *Rfrp* expression is decreased during the preovulatory period, but no activation data were reported (Clarke et al., 2012). The role of RFRP-3 neurons in relaying circadian information to GnRH neurons is further supported by an experimental protocol where female hamsters kept under constant light conditions split their locomotor activity and exhibit two daily LH surges. In these conditions, the left and right SCN oscillate in antiphase and RFRP-3 neurons are active asymmetrically in opposition to GnRH neuron activation (Gibson et al., 2008).

A recent study in female Syrian hamster demonstrated that AVP- and VIP-ergic fibers from the SCN form close appositions with RFRP-3 neurons and that a central injection of VIP decreases RFRP-3 neuronal activity in a time-dependent manner, being effective in the afternoon, but not in the morning, while central AVP had no significant effect (Russo et al., 2015). It is yet unclear, however, whether the action of VIP on RFRP-3 neurons is direct or indirect, since <10% of RFRP-3 neurons appear to express the *VPAC1* or *VPAC2* receptors (Russo et al., 2015). Altogether, these findings suggest a SCN-derived VIP daily regulation of RFRP-3 neuronal activity, at least in Syrian hamsters. Additionally, there is evidence in

female rodents that RFRP-3 neurons, similar to kisspeptin neurons (Chassard et al., 2015), are able to keep track of time intrinsically, expressing the clock protein PER1 with a peak at ZT12 (Russo et al., 2015).

Unlike kisspeptin cells, it is likely that high circulating levels of E2 are not required for the daily rhythm in RFRP-3 neurons as daily rhythms in RFRP-3/c-FOS are similar during diestrus and proestrus in Syrian hamsters (Henningsen et al., 2017). Although another report indicates that daily variation is abolished in OVX hamsters and restored in OXV+E2 animals (Gibson et al., 2008), in this study different time points were investigated and a different protocol was used, which might account for the disparity between both findings.

A number of studies are consistent with an inhibitory action of RFRP-3 on LH secretion in female mammals (Anderson et al., 2009; Kriegsfeld et al., 2006). In Syrian hamsters (Henningsen et al., 2017) and mice (Ancel et al., 2017), central RFRP administration decreases LH secretion when given around the time of the preovulatory LH surge, whereas it has no effect when given at other time points when LH secretion is low (early day of proestrus or diestrus). Therefore, decreased activity of RFRP-3 neurons in late afternoon, possibly mediated by an SCN VIP-ergic signal, associated with the inhibitory effect of RFRP-3 on LH secretion, indicates that tonic RFRP-3 inhibitory input is lifted at the time of the preovulatory LH surge (Figure 9).

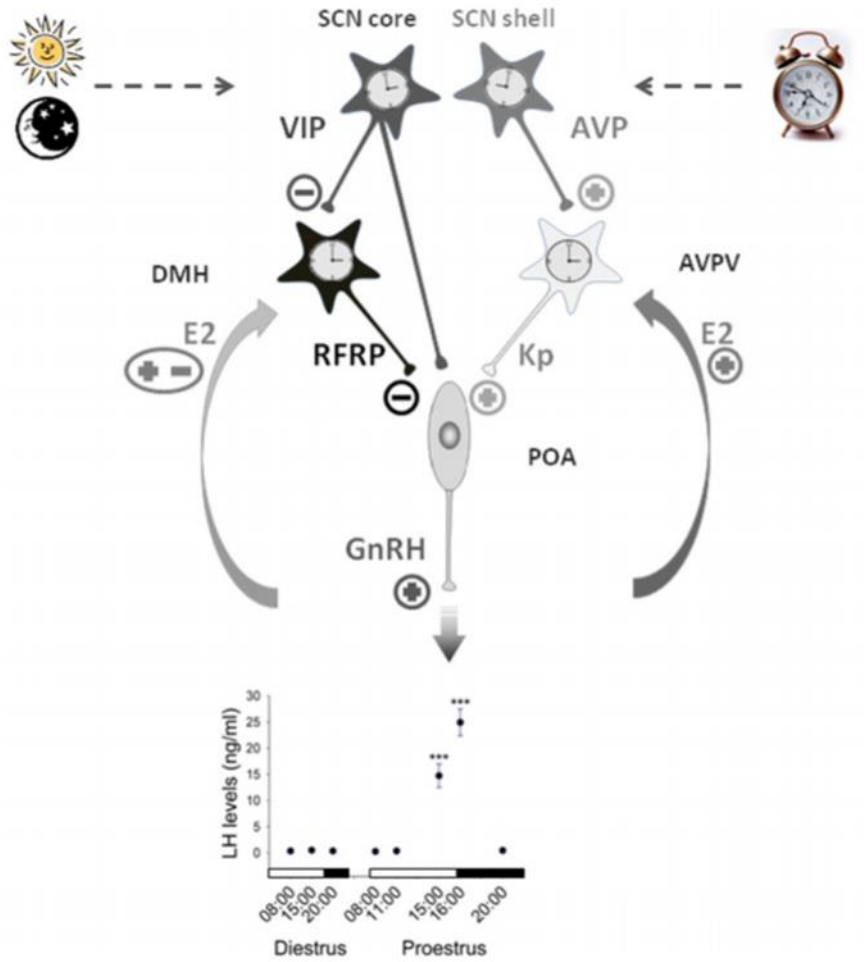

Figure 9: *Working model illustrating the contribution of RFRP-3 neurons in the central control of the daily gating of the preovulatory LH surge in female rodents. Neurons of the suprachiasmatic nuclei (SCN) synthesizing vasopressin (AVP) and vasoactive intestinal peptide (VIP) exhibit daily variation controlled by an intrinsic circadian clock and the daily change in light input. The SCN VIP output times the activity of GnRH neurons either directly and/or indirectly via the RFRP3 neurons located in the dorsomedial hypothalamus (DMH), which further inhibit GnRH neurons at the light/dark transition. The SCN AVP output activates GnRH neurons through the stimulation of neurons located in the anteroventral periventricular nuclei (AVPV) and releasing the potent stimulatory peptide kisspeptin. Additionally, kisspeptin neurons receive a positive estradiol (E2) feedback on the day of proestrus while the effect of E2 on RFRP3 neurons is still unclear. This coordinated pathway is proposed to trigger a preovulatory GnRH/LH surge at the light/dark transition of the proestrus stage. Image from (Angelopoulou et al., 2019).*

3.4 The controversy of E2 feedback on RFRP-3 neurons

The possibility that RFRP-3 neurons, similar to kisspeptin neurons (Simonneaux, 2020), may be a central site for the E2 feedback has been widely studied. However, the results obtained in different species, sex and conditions are conflicting.

ERα are found in 40% and 25% of RFRP-3 neurons in female Syrian hamsters (Kriegsfeld et al., 2006) and mice (Molnár et al., 2011; Poling et al., 2012), respectively. Studies have reported that E2 treatment in OVX Syrian hamsters increases c-FOS expression in RFRP-3 neurons (Kriegsfeld et al., 2006) while others, in contrast, show that E2 treatment decreases the amount of *Rfrp* mRNA per cell and the total amount of *Rfrp* mRNA in both male and female mice (Poling et al., 2012). In female rats, RFRP-3 neuronal activity is reported to be higher during diestrus compared to proestrus and estrous (Jørgensen et al., 2014), suggesting a role for E2 in the activational state of RFRP-3 cells across the ovulatory cycle in this species. Finally, in female rats (Quennell et al., 2010), male (Revel et al., 2008) and female Syrian hamsters (Henningsen et al., 2017), and male Djungarian hamsters (Rasri-Klosen et al., 2017), gonadectomy with/without sex steroid replacement does not have a significant effect on RFRP-3 synthesis.

On the other hand, other experimental paradigms do (indirectly) suggest a possible influence of E2 on RFRP-3 neurons. For example, E2 treatment increases RFRP-3 synthesis in the hypothalamic mHypoA-55 rat cell line (Tumurbaatar et al., 2018). In Syrian hamsters, food-restriction increases the percentage of RFRP-3 cells expressing *c-Fos*, with increased ovarian steroids at the time of estrus abolishing the impact of food restriction on RFRP-3 cellular activation (Benton et al., 2018). Finally, in female rats, RFRP-3 synthesis varies according to reproductive stage, with increased levels at the time of puberty when the endogenous sex steroid levels are highest (Quennell et al., 2010).

3.5 Concluding remarks on the role of RFRP-3 in the daily timing of the LH surge in females

Female reproduction is cyclic and in female mammals, possibly including women although this is still controversial, daily time cues are integrated within the reproductive system to coordinate the LH surge and consequential ovulation with the best period of the day. The hypothalamic SCN clock plays a key role in conveying daily information to the reproductive system, and increasing evidence indicates that RFRP-3 neurons, in addition to kisspeptin neurons, are a key relay between the SCN clock and GnRH neurons. Recent data indicate that the SCN-derived VIP output drives RFRP-3 neuronal activity, but the mechanisms involved are still unclear. Furthermore, while numerous studies now agree on the critical role of kisspeptin in the timing of LH surge, the specific significance of RFRP-3 on the occurrence of the LH surge requires further investigation.

4. The issue of altered reproduction in circadian disruption

4.1 Concept of shiftwork

The modern 24 h-functioning society requires an increasing number of employees to work outside of the natural active period. According to the International Labor Organization (ILO; 1990), working in shifts is “a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers”. Shift work and night work cover a multitude of realities: different time systems called 2 × 9, 3 × 8, 4 × 8, 5 × 8, 2 × 12 h, with variability resulting from different choices made by the employer's company.

In industrial countries, 20–30% men and 15–20% women experience shift work or work at night (Pati et al., 2001), and this is an expanding phenomenon with a particularly significant increase among women under 30 years. One difficulty to classify when work is done in shifted conditions comes from variable definitions of shift/night work, even within the European Union. Thus, in France, night work is defined as any work between 9 pm and 6 am; in Germany it is 2 h of the daily work between 11 pm and 6 am; in Italy it is a minimum of 7 consecutive hours including the timeframe between 0 am and 5 am; in Belgium it is work performed between 8 pm and 6 am; and in the United Kingdom, it is 3 h of the daily work between 11 pm and 6 am. Moreover, shift work can be defined by a number of periods, duration of the periods, shift structure (continuous or not), start and end time of work, and time between shifts.

4.2 Impact of shift work on health

An increasing number of studies report that shift work or night work is associated with increased risks of developing cardiovascular/metabolic/gastro-intestinal disorders, some types of cancer, and mental disorders including depression and anxiety (Boivin et al., 2007; Chen et al., 2010; Matheson et al., 2014). In 2007 shiftwork was reclassified from a possible to a probable human carcinogen (class 2A) by the International Agency for Research on Cancer.

Bøggild and Knutsson, 1999, who analyzed 17 studies (between 1949 and 1998), evaluated the excess risk at 40% for ischemic heart disease in shift/night workers compared to day workers (relative risk was ranging from 0.4 to 3.6, with a majority between 1 and 2). Ten years later, Frost et al. published a new review (from 16 epidemiological studies done between 1972 and 2008), which reported limited epidemiological evidence for a correlation between shift/night work and ischemic heart disease (Frost et al., 2009). More recently, a large meta-analysis (34 studies published between 1983 and 2011, including more than two million people) indicated that shift/night work is associated with a significant increase in myocardial infarction and coronary events with or without adjustment for other risk factors (Vyas et al., 2012). Since then, four other epidemiological studies have indicated an increased risk of coronary events and cardiovascular disease mortality after 5 years of shift/night work (Carreón et al., 2014; Gu et al., 2015; Hermansson et al., 2015; Park et al., 2015). Also, a causal link between shift/night work and weight gain/high body mass index is often reported, notably after 5 years, suggesting that shift/night work is a risk for type 2 diabetes (Pan et al., 2011). Indeed, a retrospective study on 6413 male shift/night workers showed an increased risk of impaired glucose tolerance (even for workers with normal and stable body weight) compared to day workers (Kubo et al., 2010). Similarly, a recent meta-analysis reported an increased risk of 1.09 between shift/night work and type 2 diabetes (Gan et al., 2015). Shift/night work is also often associated with chronic stress and a significant impact on cortisol (in humans) or corticosterone (in rodents) is well documented (Goichot et al., 1998; Gumenyuk et al., 2014; Kiessling et al., 2010; Manenschijn et al., 2011; Ulhôa et al., 2015; Weibel and Brandenberger, 2002). This is important because glucocorticoids play a major role in the circadian resynchronization of the central and peripheral clocks in a chronic jet-lag context (Kiessling et al., 2010).

Given the importance of the circadian system in the regulation of female reproduction, and given the fetal exposure to the maternal daily rhythms in temperature, hormones and metabolic cues, female shift workers may display reproductive dysregulations. Indeed a few studies have reported increased risk of irregular menstrual cycles, endometriosis, miscarriage, low birth weight or pre-term delivery in women in shift/night work conditions

(Gamble et al., 2013; Lawson et al., 2011; Rocheleau et al., 2012). Notably, an animal study showed that maternal circadian disruption during pregnancy may lead to fetal SCN clock desynchronization (Nováková et al., 2010), in accordance with the well-known fact that the functioning of fetal clocks depends on maternal hormones (Serón-Ferré et al., 2012; Torres-Farfan et al., 2011).

4.3 Modeling shift work in rodents

In order to better understand the mechanisms underlying the negative impact of shift/night work on health, it is necessary to develop a relevant animal model of circadian disruption. However, shift work is a very complex situation and therefore it is difficult to design animal model conditions that truly mimic human shift work, which is often associated with potential confounding factors (diet, social stress, sleep disturbance, use of psychostimulants). Furthermore, most studies are carried out on nocturnal animals (rats, mice, hamsters), while humans are diurnal. Apart from melatonin, whose secretion is always highest during the dark period, other hormones (cortisol/corticosterone, glucose, leptin, gonadotropins) and many biological functions (food intake, sleep/wake, cardiac functions, vigilance) have opposite rhythms between diurnal and nocturnal species. Moreover, for most of these studies only males are used to avoid an effect of the female reproductive cycles in the measurement of the circadian disturbances. Yet, animal studies are essential for understanding the cellular and molecular mechanisms underlying circadian perturbations. A recent review listed four relevant models that use altered timing of either food intake, activity, sleep or light exposure, or a combination of these (Opperhuizen et al., 2015).

Regarding female reproduction, very few animal studies have investigated alterations in fertility or LH surge timing after a shift in the light/dark cycle or photoperiod. One study in female Syrian hamsters reported that after a 3 h phase advance, the LH surge is not fully resynchronized to the new dark onset even after 3 days, but when they are submitted to a 3 h phase delay, the LH surge is synchronized more rapidly (Moline and Albers, 1988).

Furthermore, photoperiod lengthening was associated with similar shifts in locomotor activity and the LH surge in female hamsters (Moline et al., 1981). In mice, exposure to either regular phase advances or delays at the beginning and throughout pregnancy resulted in a significant decrease in pregnancy success (Summa et al., 2012) . Finally, an *in vitro* study reported that the ovarian clock was not fully resynchronized 6 days after a 6 h phase advance in PER2:LUCIFERASE mice (Yamazaki et al., 2000). Thus, despite the extensive research on the impact of circadian disruptions, the negative effects on the reproductive system have not been fully explored yet.

4.4 Concluding remarks on the effect of circadian disruption on reproduction

The female reproductive system displays changes in hormone secretion and ovulation in a cyclical and circadian manner. Although only few studies have been performed, both epidemiological investigations and animal studies indicate that circadian disruption, observed when the light/dark cycle is acutely (jet-lag) or chronically (shift work) shifted, may impair the timing of the reproductive cycles. Clearly, more investigations are required in order to determine whether and, if yes, how disruptions in the endogenous circadian timing system underlie reproductive deficiency.

5. Neuroendocrine control of reproductive senescence

5.1 Reproductive aging in females

In female mammals, reproductive activity encompasses three defined periods throughout development, the pre-pubertal period, the fertile period, and the post-menopausal unfertile period. In healthy women, puberty starts around 11 and 13 years, and menopause occurs between 45 and 53 years (Barros et al., 2019; Gold, 2011). Postponing childbirth until after the age of 35 has become a complex socio-economic phenomenon, which is increasingly evident in the last decades (Lampinen et al., 2009). Advanced maternal age is associated with a higher risk of miscarriage, preterm birth and genetic disorders of the foetus (Newburn-Cook and Onyskiw, 2005; Schmidt et al., 2012). Therefore, identifying the sequence of events preceding menopause and the mechanisms coordinating these events is of outmost importance.

In women, reproductive senescence is associated with exhaustion of primary follicles and loss of fecundity. Menopausal transition is characterized by menstrual cycle variability, wide fluctuations in reproductive hormones and eventually permanent loss of menstruation at the average age of 51 years (Santoro, 2005). In contrast, female rodents do not undergo exhaustion of the follicular pool (Mandl and Shelton, 1959), although they do demonstrate progressively irregular ovarian cycles. Reproductive aging in female rodents is marked by the onset of longer irregular estrous cycles (> 4-6 days) at the age of 8-12 months, followed by a period of constant estrous (CE) or persistent vaginal cornification at the age of 10-16 months. CE period is followed by a prolonged diestrus phase with intermittent ovulation known as repetitive pseudo-pregnancy (RPP), before reaching the anestrous stage at the age of 22-25 months (Cruz et al., 2017).

Female mammals exhibit age-dependent changes in the neuroendocrine mechanisms that control reproduction. In humans, menopausal transition is characterized by huge swings in estradiol and gonadotropin levels before reaching post menopause (Hall, 2004). The aging ovary stops responding to normal FSH signals and ceases to produce adequate levels of estrogen and progesterone, which serve as down-regulatory signals to the hypothalamus

and the pituitary. Thus, perimenopausal women exhibit increased FSH production followed by increased LH secretion, both of which are markers of reduced fertility (Fitzgerald et al., 1998). Similar to women, rodents display increased gonadotropin secretion at advanced ages (Belisle et al., 1990), even though they do not undergo depletion of the follicular pool and therefore maintain high estrogen levels (Chakraborty and Gore, 2004; Mandl and Shelton, 1959). While rodent ovarian activity progressively deteriorates (Cruz et al., 2017), the timing of the preovulatory LH surge is delayed and exhibits reduced amplitude during middle age (Nelson et al., 1982)). Despite the differences in the circulating levels of estrogen between women and female rodents during aging, the use of non-human animal models offers certain advantages in deciphering the mechanisms of reproductive decline; since the rodent HPG axis is highly conserved and estropause closely assimilates perimenopausal transition (Kermath and Gore, 2012).

5.2 Primary role of the aging hypothalamus in the induction of reproductive decline

Although for many years menopause has been attributed to ovarian failure due to the exhaustion of primary follicles, an alternative perspective is that menopausal transition is initiated by age-related alterations in the central nervous system; notably in the hypothalamus and the pituitary. However, given the extent of interactions and feedback loops between the different levels of the HPG axis, determining their relative contributions to the induction of reproductive senescence is complicated (Rubin, 2000).

Age-related alterations in pituitary physiology have been associated with reproductive decline. Epidemiological studies demonstrated that the pituitary volume decreases with age (Grams et al., 2010; Lurie et al., 1990), while the amount of unoccupied space in the pituitary fossa increases (Pecina et al., 2017). Middle-aged rodents that exhibit attenuated LH surges show decreased pituitary LH responsiveness to GnRH stimulation (Brito et al., 1994; Krieg et al., 1995). Pituitary gene expression of the gonadotropin subunits and GnRH receptors

also decreases in middle-aged rodents, with no significant difference in the gene expression of the ER and PR steroid hormone receptors (Zheng et al., 2007).

Despite the well-characterized changes in the aging ovary and pituitary, multiple studies suggest that age-related alterations in the hypothalamus precede the onset of reproductive decline. A recent epigenome-wide study demonstrated that global hypothalamic DNA methylation decreases during aging and identified changes in DNA methylation in genes encoding hormone signaling, glutamate signaling, melatonin and circadian pathways (Bacon et al., 2019). Transplantation studies showed that old rodent ovaries exhibit cyclic activity when transplanted in young females. However, young ovaries transplanted in old anestrous rodents cannot maintain regular cyclic activity (Peng and Huang, 1972). Interestingly, electrical stimulation of the hypothalamus successfully induces ovulation in old acyclic rodents (Clemens et al., 1969). A pharmacological study showed that drug administration that corrects hypothalamic deficiencies, temporarily restores estrous cyclicity in middle-aged rodents (Quadri et al., 1973).

Hypothalamic GnRH neurons, the driving force of the reproductive axis, undergo changes during senescence as well. Middle-aged rodents display a decreased number of GnRH cells and GnRH neuronal activity during the preovulatory GnRH/LH surge (Funabashi and Kimura, 1995; Lloyd et al., 1994; Miller et al., 1990; Yin et al., 2009). Whether these changes in the GnRH system are intrinsic or due to age-dependent alterations in the neural circuits that regulate GnRH activity, has not been deciphered yet.

Kisspeptin (Kp), one of the main stimulators of the GnRH system, also undergoes age-dependent changes. Postmenopausal women display an increased number and size of Kp neurons and expression of the Kp encoding gene, *Kiss1*, in the infundibular nucleus (Rometo et al., 2007). Interestingly, these phenotypes resemble the ones observed in ovariectomized primates (Eghlidi et al., 2010; Kim et al., 2009; Rometo et al., 2007). In middle-aged rodents by contrast, a decreased number of Kp cells and reduced levels of *Kiss1* mRNA expression in the AVPV during the preovulatory LH surge are observed (Lederman et al., 2010; Neal-Perry et al., 2009). Central administration of Kp in the POA restores the attenuated amplitude of the LH surge in middle-aged rodents (Neal-Perry et al., 2009). Therefore, age-

related alterations in the GnRH system may be driven in part by altered Kp signaling, along with changes in other regulatory systems extrinsic to GnRH neurons. Notably, given the reported action of RFRP-3 on the GnRH system, it is worth examining whether ageing has an impact on the RFRP-3 system.

5.3 Age-dependent alterations in the circadian system

During aging, the circadian regulation of many physiological and behavioral processes is progressively disturbed. Age-dependent alterations in circadian rhythms include decreased amplitude and period length, increased fragmentation and tendency to desynchronization (Carskadon et al., 1982; Martin et al., 1986; Rs et al., 1991; Shibata et al., 1994; van Gool et al., 1987). Earlier studies demonstrated that transplantation of fetal SCN tissue can restore age-related deficits in the circadian system (Cai and Wise, 1996; Van Reeth et al., 1994). Therefore, circadian disruptions during senescence have been associated with impairment in SCN function. Numerous studies examined the components of the SCN that could be affected by aging; including the input pathways to the SCN, the SCN molecular clock, the electrical properties of SCN neurons and the output pathways of the SCN towards the periphery (Buijink and Michel, 2020).

During aging the ability of the SCN to be entrained by light is compromised, due to major changes in the light transduction pathway towards the SCN (Lupi et al., 2012; Sutin et al., 1993). Notably, advanced age is associated with a loss in the number, density and dendritic arborization of the ipRGCs (Esquiva et al., 2017; Lax et al., 2019). Despite the well-characterized deficits in the light input pathway towards the SCN, multiple studies demonstrated that the SCN molecular clockwork is preserved during aging (Asai et al., 2001; Nakamura et al., 2011; Polidarová et al., 2017; Yamazaki et al., 2002). However, findings in the molecular clock components are not always consistent. Of note, circadian expression profiles of *Per1* and *Cry1* mRNA are maintained in the senescent SCN (Asai et al., 2001; Weinert et al., 2001), contrary to the expression of *Bmal1* that decreases with aging (Chang and Guarente, 2013; Kolker et al., 2003), while expression of *Clock* is reported to either

decrease or show no variation with age (Kolker et al., 2003; Weinert et al., 2001). Interestingly, while the expression of *Per2* remains rhythmic during senescence under normal lighting conditions, this rhythmicity is abolished under constant light or constant darkness (Nakamura et al., 2015; Polidarová et al., 2017). Electrophysiological studies in rodents revealed age-related changes in the SCN neuronal activity, including decreased amplitude of the SCN electrical activity rhythm, desynchronization of SCN neurons and aberrant SCN firing patterns (Watanabe et al., 1995; Satinoff et al., 1993; Farajnia et al., 2015, 2012; Nakamura et al., 2011). Interestingly, the activity rhythms in one of the main circadian outputs of the SCN, the subparaventricular zone (SPZ), are also decreased at advanced ages (Nakamura et al., 2011). Aging may also affect the synthesis of neuropeptides that act as synchronizers within the SCN and/or as output signals of the SCN. In humans, the SCN volume and total number of AVP cells decreases at advanced ages (Swaab et al., 1985). The daily rhythm of AVP synthesis in the human SCN is disrupted during senescence, showing loss of diurnal oscillations, reduced amplitude and reversed diurnal pattern (Hofman and Swaab, 1994). Senescent rodents exhibit no changes in the SCN volume and in the total SCN cell number (Roozendaal et al., 1987). However, the number of AVP (-31%) and VIP (-36%) neurons also decreases in the rodent SCN during aging (Roozendaal et al., 1987; Chee et al., 1988), and in middle-aged rodents rhythmicity of *VIP* mRNA levels, but not of *AVP* mRNA levels, is attenuated (Krajnak et al., 1998b).

In conclusion, while the molecular clock remains functional during aging, the amplitude of the SCN electrical rhythm and the circadian expression of neuropeptides are both impaired, probably resulting in a compromised SCN output signal. Altogether these findings suggest an age-related uncoupling between the molecular and the electrical clock components of the SCN. Therefore, other brain areas and organs might exhibit age-dependent deficits in their own endogenous clocks as well as receive a weaker systemic timing signal (Buijink and Michel, 2020).

5.4 Concluding remarks on the neuroendocrine control of reproductive aging

During aging both the reproductive and the circadian systems undergo changes. Age-related alterations in the SCN function could explain changes in behavioral and physiological functions during reproductive senescence, such as the altered sleep/wake cycles (Gómez-Santos et al., 2016; Jehan et al., 2015) and the alterations in gonadotropin secretion (Fitzgerald et al., 1998; Nelson et al., 1982). While aging admittedly compromises the SCN output signal, more research must be done in order to unravel the exact mechanism through which circadian control of the GnRH/LH surge becomes impaired during senescence.

6. Outline and scope of thesis

The aim of the present thesis is to investigate the effects of time of day, estrous stage and aging on RFRP-3 neurons and LH secretion in female mice, using neuroanatomical, electrophysiological and endocrine approaches. First, we examined whether mouse RFRP-3 neurons display daily rhythms of activity and whether there are daily- and/or estral-dependent changes in the density of AVP- and VIP-ergic fiber innervation on RFRP-3 neurons. In addition, we aimed to characterize the firing properties of RFRP-3 neurons during different time points of the day and estrous stages, and the effect of the circadian peptides, AVP and VIP, on RFRP-3 electrical activity during various time points of the day in proestrus and diestrus (Part II, chapters 2 & 3). Next, we tested the hypothesis that circadian disruptions in the light/dark cycle have a direct impact on fertility and breeding success given that ovulation and estrous cyclicity are under circadian control in female mammals. Therefore, we evaluated the effects of a single or chronic light/dark cycle phase shifts on the characteristics of the preovulatory LH surge, the estrous cyclicity and the gestational success (Part III, chapter 4).

In the last part of our study (Part IV), we investigated some endocrine and neuronal aspects of the complex physiological process that occurs in female mammals during transition to reproductive senescence. First, we performed an individual longitudinal analysis of LH secretion, by examining the timing and amplitude of the preovulatory LH surge, in order to establish a longitudinal marker of female reproductive capacity in rodents and evaluate reproductive robustness throughout adult life (chapter 5). Then, because it is still unknown whether aging in the GnRH neurons is intrinsic or due to alterations in the input from the SCN and/or in the intermediate RF-amide modulatory systems, we investigated whether there are age-dependent alterations in the RFRP-3 neuronal system and in the daily pattern of AVP- and VIP-ergic fiber input on RFRP-3 neurons and whether they correlate to changes in the LH production (chapter 6).

Abbreviations

ARC: arcuate nucleus

AVP: arginine-vasopressin

AVPV: anteroventral periventricular nucleus

[Ca2+]i intracellular calcium concentration

CRY: cryptochrome

CT: circadian time

DMH: dorsomedial hypothalamus

E2: estradiol

FSH: follicle-stimulating hormone

GnIH: gonadotropin inhibitory hormone

GnRH: gonadotropin releasing hormone

HPG axis: hypothalamo-pituitary-gonadal axis

HPO axis: hypothalamo-pituitary-ovarian axis

ipRGCs: intrinsically photoreceptive retinal ganglion cells

Kp: kisspeptin

LH: luteinizing hormone

ME: median eminence

NPY: neuropeptide Y

PER: period

POA: preoptic area

RFRP-3: (Arg)(Phe)-amide peptide 3

SCN: suprachiasmatic nucleus

TTFLs: transcriptional-translational feedback loops

VIP: vasoactive intestinal peptide

VMH: ventromedial hypothalamus

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