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Daily rhythms count for female fertility

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Female ovulation depends on a surge in circulating luteinizing hormone (LH) which occurs at the end of the resting period and requests high circulating estradiol. This fine tuning involves both an estradiol feedback as an indicator of oocyte maturation, and the master circadian clock of the suprachiasmatic nuclei as an indicator of the time of the day. This review describes the mechanisms through which daily time cues are conveyed to reproductive hypothalamic neurons to time the pre-ovulatory surge. In female rodents, neurotransmitters released by the suprachiasmatic nuclei activate the stimulatory kisspeptin neurons and reduce the inhibitory RFRP neurons precisely at the end of the afternoon of proestrus to allow a full surge in LH secretion. From these findings, the impact of circadian disruptions (during shift or night work) on female reproductive performance and fertility should now being investigated in both animal models and humans.

A dedicated hypothalamic network controls reproductive activity

Gonadal activity depends primarily on a set of neurons located in the hypothalamus and producing the gonadotropin releasing hormone (GnRH). These neurons are scattered in the preoptic area and the

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vascular organ of the lamina terminalis, but they mostly project at the median eminence where they release GnRH into the portal blood to further activate the synthesis and release of two gonadotropins, luteinizing (LH) and folliculo-stimulating (FSH) hormones, from the pituitary gonadotrophs. In females, FSH promotes follicular growth and sex steroid production while LH triggers ovulation of the mature follicules when the circulating level of estradiol is high enough to attest follicle maturation.

Various (neuro)transmitters have been proposed to regulate GnRH neuronal activity, but in 2003, the finding that mutations in the gene encoding the receptor of kisspeptin (Kiss1R, formerly GPR54) induces idiopathic hypogonadotropic hypogonadism in humans and mice [1,2] shed light on the pivotal role of kisspeptin on the regulation of GnRH neurons. The Kiss1 gene encodes a family of peptides generated from an initial 145 amino acid kisspeptin (Kp) propeptide, Kp145, which is cleaved into peptides of different sizes from Kp54 (previously named metastin) to Kp10. The discovery of Kp and its major role in reproductive function have been a milestone in the field of reproductive biology. An increasing number of studies now indicate that Kps are critical regulators of sexual differentiation and maturation as well as of normal adult reproductive functioning across mammalian species, including humans [3]. Kp neurons are localized within two hypothalamic areas, in the arcuate nucleus (ARN) and the rostral periventricular nucleus of the third ventricle, also called anteroventral periventricular nucleus (AVPV), or the preoptic area (depending on species). They send projections mainly to the GnRH neuron cell bodies (AVPV Kp neurons) and nerve terminals (ARN Kp neurons) [4–6]. Importantly, AVPV presents a marked sexual dimorphism with much more Kp neurons in females and it plays a specific role in driving the pre-ovulatory GnRH/LH surge [4,7,8]. Kiss1R is highly expressed in GnRH neurons but also in other brain areas and in endocrine tissues like the pituitary gland, ovary, and placenta [9–11]. Kp has a very potent stimulatory action on GnRH release and therefore gonadotropin secretion in all mammalian species investigated so far [12–15]. Central injection of doses as low as 0.1–1 pmole Kp10 is sufficient to evoke robust LH secretion in rodents and primates [13,15]. The essential role of the Kiss1/Kiss1R complex in the central regulation of the gonadotropic axis is attested by the profound impaired reproduction (abnormal sexual maturation, small uterus, ovaries without mature follicles, no estrous cycle) associated to mutations in Kiss1 [16,17] or Kiss1R [1,18,19] in mammals, including humans.

Other neurotransmitters and hormones have been reported to regulate GnRH neuron activity, albeit not to the same extent as Kp, such as glutamate which stimulates Gnrh gene expression and GnRH release during the LH surge [20,21] and nitric oxide (NO) which has been reported to coordinate GnRH neuronal activity [22]. Notably, recent studies indicate that another neuropeptide belonging to the same RF-amide peptide family as Kp, RFRP-3 (the mammalian homolog of avian gonadotropin inhibitory hormone (GnIH)), acts at several central sites to regulate reproductive activity. RFRP-3 is encoded by the Rfrp gene (also encoding RFRP-1 with moderate if any effect on the reproductive axis) expressed in neurons exclusively located in the dorsomedial hypothalamus [23]. RFRP neurons project to various brain areas including the preoptic area and within the vascular organ of the lamina terminalis (OVLT) where RFRP fibers make contact with GnRH neurons and the AVPV/medial preoptic nucleus where RFRP fibers make contact with Kp neurons [23–25]. The main RFRP-3 binding site is reported to be the receptor GPR147 (also known as NPFF1R), but it is possible that other receptors are activated by RFRP-3 due to cross reactivity to other RF-amides receptors [26]. GPR147 is expressed in various brain areas notably those related to the central control of reproduction. Thus a significant number of GnRH neurons (15–33%) and Kp neurons (5–25%) express GPR147 [24,27]. Further, electrophysiological investigation on mouse hypothalamic sections has demonstrated a direct effect of RFRP-3 on GnRH neuronal firing rate with either inhibitory (41%) or stimulatory (12%) action [28]. Unlike Kp, RFRP-3 is mostly reported to inhibit reproductive activity [23,29,30]. However, recent studies have revealed a sex-dependant effect of the peptide. Thus in Syrian hamsters and mice, a central injection of RFRP-3 increases GnRH neuronal activity and LH secretion in males, whereas in females it reduces the amplitude of the LH surge [23,31,32]. Moreover, RFRP-3 appears to have an additional direct hypophysiotropic effect in ewes [29], although this is still disputable in rodents.

The critical role of the sex steroid feedback

Sex steroids produced by the gonads have long been known to feedback on the hypothalamo-pituitary axis in order to exert a retrocontrol of reproductive activity. In males, testosterone exerts a

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