ROLE OF THE PINEAL GLAND, ENDOGENOUS OPIOIDS AND NEUROPEPTIDES IN REPRODUCTION

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DOI: https://doi.org/10.5281/zenodo.15014297

INTRODUCTION

The pineal governs or participates in the command of many bodily functions by means of its endocrine action, using mechanisms and physiological correlations that are presently not fully explained. Investigations in both animals and humans have provided evidence that the gland plays an important role in the regulation of both the circadian and seasonal rhythms in a variety of species (Masson Pevet and Gauer,1994). It recently was shown that the gland has a significant role in regulating the seasonal reproductive behaviors of animals that breed seasonally. Primarily in follicular growth, melatonin and its receptors are essential for controlling the animal reproductive mechanism. It is unknown, meanwhile, how melatonin affects the regulation of hormones involved in reproduction (Talpur *et al*., 2018). The discovery that arcuate dynorphin neurons that coexpress kisspeptin along with neurokinin B (NKB), also referred to as kisspeptin/neurokinin B/dynorphin (KNDy) neurons, function as the primary controller of pulsatile gonadotropin-releasing hormone (GnRH) production in animals has drawn focus on endogenous opioid peptides as essential neuropeptides in the central mechanism controlling female reproduction (Tsukamura, 2022).

ROLE OF THE PINEAL IN REPRODUCTION

Single endocrine gland that is directly affected by the outside world through the retina is the pineal body, which really transforms environmental cues into neuroendocrine responses. Among the two males and females, the capacity for reproduction exhibits qualitative and quantitative variations associated with the seasonal cycle, particularly during the summer and winter seasons. This characteristic is particularly noticeable in animals that breed seasonally, as modifications in their reproductive cycle indicate that their reproduction is synchronized with shifts in the photoperiod (Tamarkin *et al*.,1995). Seasonal variations between different species regarding reproductive functions are controlled by their pineal by means of its hormonal activity, which is synced with the light-dark cycle (Weaver *et al*.,1993).Studies showing that pinealectomy and superior cervical ganglionectomy (SCGx) disrupted normal reproductive responses during variations in artificial and natural day lengths set up the pineal's function. A significant secretory product of the pineal, melatonin is thought to have a role in measuring photoperiodic time. Melatonin levels in the blood fluctuate according to fight-dark cycles, with production being noticeably higher during the dark. Photo-refractoriness is linked to a disturbance in the melatonin rhythm. Additionally, normal, pinealectomized, and SCGx animals exhibit equivalent reproductive effects of melatonin treatments that replicate secretory patterns under long or short days. Instead of creating reproductive cycles, the pineal gland and melatonin synchronize endogenous reproductive rhythms with light-dark cycles. These findings led to the conclusion that light controls the onset and offset of melatonin, regulating the circadian rhythm and determining the length of time rams secrete melatonin (Maeda and

Lincoln,1990). The significantly elevated expression of MLT and its two membrane receptors (MT1 and MT2) in the ovaries of many mammals, including humans, rats (Soares *et al*.,2003), as well as in cattle (Wang *et al*.,2012) and mice (Lee *et al*., 2001) has been documented in a number of earlier investigations. Follicle growth, oocyte maturation process , luteinization, and early development have all been demonstrated to be significantly influenced by melatonin (Basini *et al*.,2017) . The majority of melatonin's cell action seems to be controlled by its capacity to bind to its G protein-coupled receptors, MT1 and MT2, increasing G protein activity in the process. It is demonstrated in a recent research investigation that MLT/MT1 controls luteinizing hormone (LH) and, in turn, luteinization in the ovaries of mice and cows (He *et al*.,2016). It is generally accepted that melatonin regulates ovarian function by directing the production of gonadotrophin by the hypothalamus-pituitary gland axis via specific receptors (Tian *et al*.,2017).

Additionally, the combining effect of FSH and melatonin has recently examined on pre-antral follicle growth of caprine, in vitro, and the result suggested that the participation of FSH and melatonin was crucial for integrity and growth of follicles (Rocha *et al*.,2013). Melatonin therapy delayed the onset of sexual maturity and impaired ovarian development in female animals (Basheer *et al*.,2016) . Even though the fact that male mice given exogenous melatonin showed reduced testis proportions (Johnston *et al*.,2006). Melatonin binds to specific receptors inside the testes to unwaveringly regulate testicular development (Lima *et al*.,2016). Furthermore, the whole capacity and superficial region of the mitochondria as well as endoplasmic reticulum in the mice Leydig cells were significantly reduced by melatonin administration. This is noteworthy since these organelles are essential locations for enzymes involved in androgen production (Redins *et al*.,2002). Rats given melatonin had reduced testes and fewer spermatids, according to histological and ultrastructural analyses (Rashed *et al*.,2010). Several species semen contains melatonin receptors, suggesting that it may have an physiological role in regulating semen functions (Van *et al*.,1992).The quality of embryos created in vitro is enhanced by melatonin amid the maturation and embryonic development of cow and buffalo oocytes (Cordeiro *et al*.,2017).These findings showed how crucial that underlies melatonin rhythms are for measuring photoperiodic time and how these are relate to reproductive behaviors, thus Melatonin is essential for the regular physiological processes involved in animal reproduction.

ROLE OF THE ENDOGENOUS OPIOIDS AND NEUROPEPTIDES IN REPRODUCTION

Some of the most fascinating developments in reproductive neuroendocrinology within the past 20 years has been the identification of KNDy neurons. In Different species it have been confirmed that dynorphin, neurokinin B (NKB), and kisspeptin coexpression occurs in a population of ARC neurons (Uenoyama *et al*.,2020). The following is the most likely explanation for the cellular process controlling synchronized KNDy neural activity to produce GnRH pulses: According to our theory, dynorphin from KNDy neurons stops KNDy neuronal activity through the inhibitory Gi/o coupled KOR, NKB starts synchronized KNDy neuronal activity by triggering the release of kisspeptin via stimulatory Gq-coupled NK3R, and kisspeptin then triggers the release of GnRH through stimulatory Gq-coupled GPR54 expressed in GnRH neurons (Ikegami *et al*.,2021). In Kiss1-knockout female rat species, restoring Kiss1 expression in 20–50% of ARC NKB neurons could restore pulsatile LH release and folliculogenesis all the way up to the preovulatory follicles. These results offer concrete proof that the GnRH pulse generator in female mammals originates intrinsically from ARC KNDy neurons (Nagae *et al*.,2021).

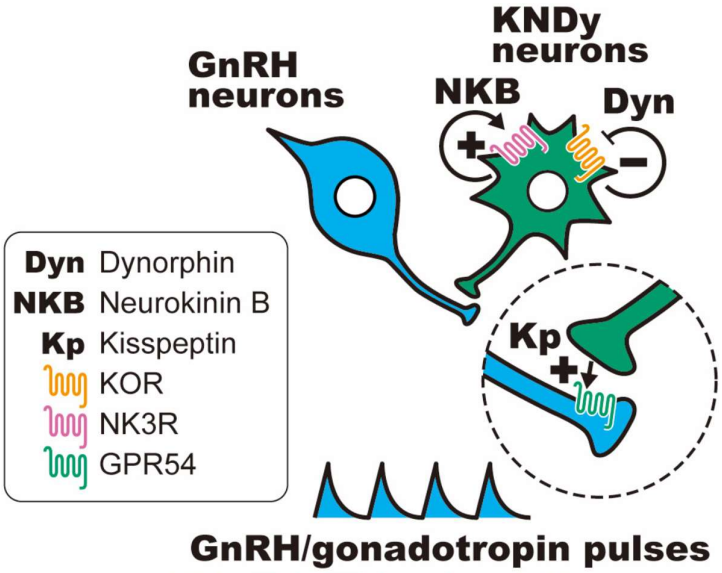

Fig: Schematic illustration of the hypothetical mechanism of gonadotropin-releasing hormone (GnRH) pulse generation in female mammals.(Uenoyama *et al*.,2020)

Tyr-Gly-Gly-Phe-Met (also known as Met-enkephalin) along with Tyr-Gly-Gly-Phe-Leu (also known as Leu-enkephalin) are two pentapeptides that were discovered in pig brains in 1975 as endogenous ligands for opiate or morphine receptors (Hughes *et al*., 1975a,b). The presence of the Met-enkephalin motif on the N terminus of beta-endorphin, another endogenous opioid peptide, was quickly discovered in 1976 (Li and Chung, 1976). The dynorphin family, met- and leuenkephalins, and β-endorphin have been demonstrated to share three different types of opioid receptors: μ-, δ- and k-opioid receptors (MOR, DOR, and KOR), which are produced through the genes *Oprm*1, *Oprd*1, and *Oprk*1, respectively (Stein, 2016). In female mammals, we imagine that opioidergic neurons act as mediators of inhibitory internal and external stimuli, such as stress, levels of nutrition, or ovarian steroids, on the release of tonic GnRH/gonadotropin. It is commonly known how the negative feedback action of ovarian steroids, which includes progesterone (P4) and estradiol-17b (E2), regulates the frequency of GnRH/gonadotropin pulses. This keeps circulating levels of LH and FSH at appropriate levels to support follicular development during the follicular phase of the estrous/menstrual cycle and preserve corpus luteum function during the luteal phase and pregnancy period. Endogenous opioid peptides could regulate the negative feedback impact of gonadal steroids over tonic GnRH/gonadotropin secretion in female animals (Uenoyama *et al*.,2020). According to Ebling *et al*. (1989), the estrogen-negative feedback effect on pre-pubescent restrictions of sexual activity is mediated by endogenous opioidergic signaling. In the ARC of lambs, Aerts *et al*. (2021) observed pubertal increases in Pdyn and Kiss1 expression in contrast to Tac3.These outcomes imply both Kiss1 and dynorphin-KOR signaling, which are parts of KNDy neurons, are important modulators of GnRH pulse production in female animals at the start of puberty. The two E2 and P4 raised Pomc mRNA levels within the ARC of OVX ewes, revealing the negative feedback effect of ovarian steroids on pulsatile GnRH/gonadotropin secretion, surely in sheep, could be mediated by ARC β-endorphin neurons. When combined, the results imply a stress-induced reduction of tonic GnRH/gonadotropin production in female animals and the negative feedback action of ovarian steroids may be mediated by dynorphin-KOR signaling in the majority of

KNDy along with GnRH neurons (Uenoyama *et al*.,2022). Additional research is required to elucidate the specific opioidergic neural pathways that regulate KNDy and GnRH neuronal activity in female animals in order to determine the precise involvement of hypothalamic opioidergic neurons in animal reproduction overall.

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Cite this article:
Aashish1, Ravi Kumar Yadav2. (2025). Role of the pineal gland, endogenous opioids and neuropeptides in reproduction. Vet Farm Frontier, 02(02), 65–69. https://doi.org/10.5281/zenodo.15014297.