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Publication Date

2020-05-01

DOI

10.1016/j.mce.2020.110781

Peer reviewed

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HHS Public Access
Author manuscript
Mol Cell Endocrinol. Author manuscript; available in PMC 2021 February 12.

Published in final edited form as:
Mol Cell Endocrinol. 2020 May 01; 507: 110781. doi:10.1016/j.mce.2020.110781.

Editorial: Hormone release patterns in mammals

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Abstract

Many physiological systems rely on hormones to communicate and time cellular and tissue-level functions. Most endocrine systems are dynamic and governed by complex regulatory systems and/or feedback mechanisms to generate precise patterns and modes of hormone release in order to optimize control of physiological and cellular processes. This Special Issue focuses on hormone release patterns (ultradian, infradian, pulsatile, circadian), with a special emphasis on the hypothalamic-pituitary axis as well as melatonin release, and how these patterns of hormone secretion change during life stages and disease.

Keywords

Hormone; Release; Secretion; Pulses; Anterior pituitary; Hypothalamus; Pineal; Melatonin; Neuroendocrine

1. Introduction

The brain plays an important role as integrator of environmental and physiological status. At the center of this “homeostasis” integration center is the hypothalamus (Levine, 2000, 2012). Hypothalamic neurons are under the regulation of both hormonal and neural input and project to numerous brain regions, including the pineal gland, which releases melatonin, as well as the median eminence to govern anterior pituitary hormone secretion. With respect to the latter, in this Special Issue we collate focused reviews on secretion patterns of prolactin, adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and growth hormone (GH). Each of these hormones are released in specific patterns which are often augmented by numerous factors including time of day, age, sex, and physiological condition (stress, pregnancy, metabolic state, disease, etc.).

The field of neuroendocrine research, and particularly the hypothalamic-pituitary connection, lagged for a long time behind the study of many other endocrine systems due to the difficulty in identifying and measuring peptide hormone levels in the nano and picogram

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ranges. These challenges were overcome in the 1950s when Dr. Yalow and colleagues developed the radioimmunoassay (RIA) allowing the detection of peptide hormones in the picogram range. Dr. Yallow was awarded the Nobel Prize in Physiology or Medicine in 1977 (Meites, 1977) for the development of the RIA, alongside Drs. Guillemin and Schally for their fundamental advances of brain “releasing factors”, today generally known as neurohormones. Together, these developments laid the foundation for today’s research of hypothalamic and pituitary function and neuroendocrinology in general. In addition to RIA, which revolutionized the study of peptides and other small molecules at very low concentrations, other major technological advancements over the last decade have provided scientists with high sensitivity enzyme-linked immunosorbent assays (ELISA) that further permit reduced sample volume, while still retaining a somewhat high sensitivity. These technological innovations are increasing our understanding of the complex patterns of hormone release *in vivo*, even in small model organisms, such as mice, in which this was not previously technically feasible. Moreover, some studies are even starting to combine detailed hormone release analyses with *in vivo* neuronal activity recordings (Han et al., 2015; Kenealy et al., 2017), adding a new level of resolution to our understanding of neuroendocrine function and regulation. The nine review papers in this Special Issue focus on different mechanisms underlying the generation and regulation of hormone release patterns, and discuss how some secretion patterns adapt to pregnancy (prolactin, melatonin), estrous cycle and menopause (FSH, LH), aging (GH), fasting (GH), disease (LH in polycystic ovary syndrome, PCOS), environmental changes in day length (melatonin and prolactin), and stress (LH and ACTH). Each hormone is influenced by specific feedback and/or regulatory mechanisms that finetune its release pattern through alterations in frequency, amplitude (concentration), and/or the time of day of secretion. The information carried by the hormone patterns is then decoded by target tissues to elicit proper physiological responses to the environment or circumstance.

The 1st review by Phillipps et al. (2020), is on prolactin, a hormone secreted by the anterior pituitary from lactotroph cells. Prolactin is a good example of a pituitary hormone with a non-standard regulatory mechanism that requires disinhibition of lactotrophs from tonic repression by neural dopamine, and which plays different roles in male and female physiology. As its name indicates, it was initially identified to be involved in milk production and milk ejection. However, as discussed in this review, prolactin’s role in the body is much broader than lactation and is involved in a myriad of functions, including male and female reproduction. In the 2nd review Dr. Gorman (2020) discusses another hormone with a less than traditional regulatory mechanism, melatonin. In contrast to the other hormones of interest in this Special Issue, melatonin is not secreted from the pituitary, but rather is produced and released by the brain’s pineal gland under the influence of the light-dark cycle and the circadian system. Dr. Gorman summarizes our understanding of melatonin regulation and function in both seasonal and non-seasonal animals, with an emphasis on changes in melatonin release patterns throughout life. Among its multi-faceted roles, melatonin is thought to be an important circadian entraining signal for peripheral tissues and also regulates cell proliferation. Limits and short comings of studies administering exogenous melatonin are discussed and provides an interesting perspective on study design for hormones with circadian release patterns. The 3rd review by Dr. Huang et

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al. (2019) expands on sexual dimorphic hormone release patterns, this time exemplified by GH. The authors discuss how sex differences in GH release patterns originate at the level of the hypothalamus and how specific GH release patterns ultimately drive tissue-specific responses. Examples of how GH secretion changes differently in males and females, for example, in response to food restriction illustrate how important it is to study neuroendocrine functions in both sexes.

The 4th review by Focke and Iremonger (2020) centers on the hypothalamic-pituitary-adrenal (HPA) axis, the primary axis regulating stress responses. This review discusses our current understanding of the mechanisms driving ultradian and circadian release patterns of ACTH and corticosteroids. The rhythms of ACTH and corticosteroids are important in numerous processes, including metabolism and stress responsiveness. Activation of the HPA axis also strongly impacts reproductive function and LH release, a pituitary hormone required for male and female reproductive function. The complex interaction between the stress (HPA) and reproductive (hypothalamic-pituitary-gonadal, HPG) axes is reviewed in the 5th paper by McCosh et al. (2019). This review discusses the latest advances in our understanding of the neuronal and endocrine mechanisms governing LH pulse patterns during stress. This review specifically focuses on how different stressors (metabolic, psychosocial, and immune stress) engage different neuronal circuits and signaling factors to complement and mediate corticosteroid inhibition of LH pulses. The pivotal role of LH in reproductive function is further highlighted in the 6th review by Drs. Sen and Hoffmann (2020). Here the authors emphasize the contribution of cell endogenous circadian rhythms, primarily illustrated by the clock genes BMAl1 and CLOCK, in the regulation of the HPG axis and reproductive hormone release. The authors discuss how molecular clock transcription factors contribute to the function of multiple reproductive tissues and cell types throughout the body, including specific hypothalamic neuronal populations, the pituitary, uterus, ovary, and testis.

Keeping on the topic of reproduction, one step “upstream” from LH and the pituitary lies the hypothalamus, where a critically important endocrine output is gonadotropin-release hormone (GnRH). GnRH is uniquely released at the median eminence in acute pulses, the frequency of which varies and dictates the balance of LH and FSH secretion from the pituitary (Burger et al., 2008; Stamatiades and Kaiser, 2018). In the 7th review, Dr. Terasawa provides an update on how GnRH pulsatility is generated and the role of both the hypothalamic arcuate nucleus and neuropeptide Y in GnRH pulse pattern generation. The critical role of GnRH in regulating FSH release is further discussed in the 8th review by Drs. Padmanabhan and Cardoso (2020). Here, the regulation of FSH release patterns and the role of different FSH isoforms during the female reproductive lifespan, as well as advances in our understanding of FSH regulation of bone mass and adiposity, is discussed. The authors highlight current limits in the study of FSH release patterns due to short half-life of certain FSH isoforms and the lack of assays that efficiently distinguish FSH isoforms. The 9th and final review by Drs. Coyle and Campbell (2019) brings together the importance of precise hormone release, and shows how PCOS, a reproductive neuroendocrine disorder, is associated with deregulated HPG axis function. This review highlights the complexity of endocrine diseases like PCOS and discusses how abnormal GnRH and LH pulse frequency drives unhealthy downstream changes in ovarian function and steroid release.

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2. Conclusion

Collectively, these nine reviews provide an update of our current understanding of the contribution of neuroendocrine communication to generate unique patterns of hormone secretion and how these release patterns are impacted during life and disease or under different environmental conditions.

Acknowledgements

This work was supported by Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Numbers R00HD084759 (H.M.H), and R01 HD090161 (A.S.K).

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