Accepted Manuscript

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PII: S0303-7207(17)30401-X

DOI: 10.1016/j.mce.2017.07.028

Reference: MCE 10027

To appear in: *Molecular and Cellular Endocrinology*

Received Date: 6 April 2017

Revised Date: 27 July 2017

Accepted Date: 27 July 2017

Please cite this article as: Voliotis, M., Garner, K.L., Alobaid, H., Tsaneva-Atanasova, K., McArdle, C.A., Gonadotropin-releasing hormone signaling: An information theoretic approach, *Molecular and Cellular Endocrinology* (2017), doi: 10.1016/j.mce.2017.07.028.

Gonadotropin-releasing hormone signaling: an information theoretic approach.

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Abstract.
Gonadotropin-releasing hormone (GnRH) is a peptide hormone that mediates central control of reproduction, acting via G-protein coupled receptors that are primarily G_q coupled and mediate GnRH effects on the synthesis and secretion of luteinizing hormone and follicle-stimulating hormone. A great deal is known about the GnRH receptor signaling network but GnRH is secreted in short pulses and much less is known about how gonadotropes decode this pulsatile signal. Similarly, single cell measures reveal considerable cell-cell heterogeneity in responses to GnRH but the impact of this variability on signaling is largely unknown. Ordinary differential equation-based mathematical models have been used to explore the decoding of pulse dynamics and information theory-derived statistical measures are increasingly used to address the influence of cell-cell variability on the amount of information transferred by signaling pathways. Here, we describe both approaches for GnRH signaling, with emphasis on novel insights gained from the information theoretic approach and on the fundamental question of why GnRH is secreted in pulses.

Key words: GnRH, GPCR, NFAT, ERK, mathematical modeling, mutual information.

The Gonadotropin-releasing hormone (GnRH) signaling network

GnRH mediates control of the reproductive system by the CNS. It is a decapeptide hormone that is secreted by hypothalamic neurones into the hypothalamo-hypophyseal portal system and then binds GnRH receptors (GnRHR) on pituitary gonadotropes. It stimulates these cells to synthesise and secrete the gonadotropin hormones, luteinising hormone (LH) and follicle-stimulating hormone (FSH). These pituitary hormones are exocytotically secreted and control gonadal production of gametes and sex steroids. Within seconds of stimulation, GnRH causes fusion of secretory vesicles (containing LH and/or FSH) with the plasma membrane but in the long-term it also increases gonadotropin synthesis, thereby controlling vesicle LH and FSH content. GnRHR are G-protein coupled receptors (GPCRs) that signal primarily via heterotrimeric G-proteins of the G_q, family. Their activation by GnRH drives generation of the second messengers IP_3 (inositol 1,4,5 trisphosphate) and diacylglycerol. IP_3 acts via IP_3 receptors (that are ligand gated Ca^{2+} channels) located on intracellular stores (primarily the endoplasmic reticulum) to mobilize Ca^{2+}. This is followed by Ca^{2+} influx, largely via L-type voltage-gated Ca^{2+} channels, and it is the consequent increase in cytoplasmic Ca^{2+} concentration that is the main drive for the regulated exocytotic LH and FSH secretion (1-3). GnRHR also mediate activation of MAPK (mitogen-activated protein kinase) cascades, causing a largely protein kinase C (PKC)-mediated activation of the MAPK ERK (extracellular signal-regulated kinase) (4-6). GnRH influences expression of many genes in gonadotropes and gonadotrope-derived cell lines (7,8). Notably, it drives transcription of the gonadotrope signature genes (encoding αGSU, LHβ, FSHβ and GnRHR) (3,9,10) all of which can be influenced by activation of PKC and/or ERK (3,10-12). Several Ca^{2+}-regulated proteins are activated by GnRH and can also mediate transcriptional effects of GnRH. These include not only the conventional isoforms of PKC, but also the ubiquitous Ca^{2+} sensor calmodulin (CaM), as well as calmodulin-dependent protein kinases (CaMK), the calmodulin dependent phosphatase calcineurin, and one of its major effectors, the Ca^{2+} dependent transcription factor NFAT (nuclear factor of activated T-cells) (3,13,14). This brief overview omits