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Authors response to communication about mathematical modeling of gonadotropin-releasing hormone signaling

Amitesh Pratap, Kathryn L. Garner, Margaritis Voliotis, Krasimira Tsaneva-Atanasova, Craig A. McArdle

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Authors response to communication about mathematical modeling of gonadotropin-releasing hormone signaling.

In a recent review (1), we described mathematical models that we have used to explore cellular responses to dynamic stimulation by GnRH and, in a letter to the Editor, Prof. George Fink queries the relevance of our modelling to GnRH physiology. The letter provides an excellent overview of early literature demonstrating the importance of sex steroid feedback (for modulation of GnRH secretion from the hypothalamus and GnRH action on gonadotropes) as well as the self-priming phenomenon (in which a pulse or pulses of GnRH increases the secretory response to a subsequent pulse) and its likely involvement in the pre-ovulatory gonadotropin surge. Whilst we agree entirely, that these aspects are crucial for understanding hormonal control of mammalian reproduction, neither were considered in our modelling. Rather, our aim was to understand GnRH pulse frequency decoding, specifically, the fact that for some GnRH effects on gonadotropes, maximal responses are observed at sub-maximal pulse frequency, creating characteristic non-monotonic (bell-shaped) frequency-response relationships. The precise nature of these curves depends on the system output measured as maximal effects of pulsatile GnRH on FSHβ mRNA levels occur at lower pulse frequency than those for effects on LHβ so the non-monotonic frequency-response curve for FSHβ is left shifted compared to that for LHβ (2,3). Prof. Fink raises the concern that we appear to ignore the conclusion of Yen et al. (1972) (4) that "…ovarian steroids modulate the frequency and magnitude of the periodic release of gonadotropins by the pituitary gland". We would argue that, far from ignoring this conclusion, our work is largely driven by it, as we try to understand how such changes are interpreted by gonadotropes. We believe that sensitivity to GnRH dynamics is central to the physiology of the system so that our attempts to understand them in molecular and mathematical terms are, indeed, physiologically relevant.

To date we have not considered particularly complex GnRH inputs, focussing instead on varying pulse amplitude, frequency and width with a square wave GnRH pulse. Nonetheless, the model could certainly also be used to consider more complex dynamic inputs, such as a GnRH surges in which pulse amplitude, frequency, width and nadir could all vary over time. An obvious problem here would be the lack of corresponding wet-lab. data. Indeed, the availability of live cell imaging data (i.e. for effects of GnRH pulses on cytoplasmic Ca^{2+} and activation of ERK and NFAT) along with the extensive literature on pulsatile GnRH effects on gene expression, was essential for training and validation of our model, and comparable data are not available for GnRH surges. Instead, one could shift emphasis to modelling of gonadotropin secretion and although our published model does not incorporate this, we have extended it in unpublished work to include Ca^{2+} -driven secretion. This would also be essential for consideration of the self-priming where the key wet-lab data are from studies of gonadotropin secretion. Indeed, self-priming has already been modelled mathematically by consideration of two pathways with different kinetics; a fast pathway reflecting Ca^{2+}-driven exocytotic secretion of LH and a slower pathway that could reflect either cAMP-mediated hormone synthesis (5) or the recruitment of secretory vesicles from a less readily releasable pool (6). This could readily be incorporated into our published model allowing GnRH to drive two responses (exocytosis and gonadotropin synthesis of vesicle recruitment) with different kinetics. Our mathematical model was trained initially against data from HeLa cells with heterologously expressed GnRHR, and subsequently against data from gonadotrope lineage LβT2 cells. However, unlike normal gonadotropes, neither of these contain large numbers of gonadotropin secretory vesicles and neither show robust acute exocytotic responses to GnRH. Accordingly, extension of the mathematical model to consider exocytotic gonadotropin secretion would likely require training and validation against primary pituitary cell culture or in vivo data and, where emphasis is shifted to