Mathematical modelling of adult GnRH neurons in the mouse brain and its bifurcation analysis

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Abstract

Gonadotropin-releasing hormone (GnRH) neurons are cells in the hypothalamus that produce GnRH, one of the major hormones that controls fertility and reproduction. However, despite their importance, little is known about the mechanisms by which GnRH is produced. GnRH neurons exhibit complicated membrane potential dynamics, in the form of electrical bursting, and this bursting is closely coupled to the dynamics of intracellular calcium (Ca^{2+}) in ways that are not yet well understood.

A mathematical model has been constructed to help understand the mechanisms underlying the observed behaviours of GnRH neurons, and how electrical bursting synchronizes with transients in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$). Simulations show that the model is consistent with all of the most important experimental data involving TTX (tetrodotoxin), zero extracellular-$[Ca^{2+}]$ ($[Ca^{2+}]_e$) solution, apamin, CPA (cyclopiazonic acid) and 2-APB (2-aminoethoxydiphenyl borate). The mathematical model predicted the existence of particular $[Ca^{2+}]_{cyt}$-activated potassium (K^+) channels ($sI_{AHP-UCL}$), which were then confirmed experimentally. In contrast to the apamin-sensitive $[Ca^{2+}]_{cyt}$-activated K^+ channels (sI_{AHP-SK}), which control both the structure of firing within bursts and the interburst intervals, $sI_{AHP-UCL}$ solely determines the interburst dynamics. Furthermore, we show how a fast-slow bifurcation analysis of the model can be used to understand the behaviour of the cells under a wide range of experimental conditions.

The high complexity of the initial GnRH neuron model prompted us to develop a much simpler bursting model based on the FitzHugh-Nagumo (FHN) model. This simplified bursting model exhibits the similar qualitative behaviour as our initial GnRH neuron model. The use of bifurcation analysis with the FHN model simplifies the

simulation of bursting, and the results of this analysis are also briefly explained.

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