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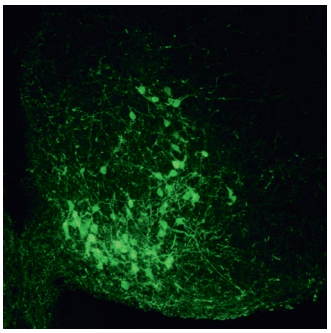
A fresh look at kisspeptin neuron synchronization



The arcuate kisspeptin neuron population in a coronal brain slice. Image courtesy of the Herbison laboratory.

For many years, the 'KNDy hypothesis' has been the main mechanistic explanation of the pulsatile secretion of gonadotropin hormones. New research in *Cell Reports* proposes an alternative mechanism.

The arcuate nucleus kisspeptin (ARN^{KISS}) neuronal network is a key part of the pulse generator. The KNDy hypothesis suggests that this network is regulated by an interplay between kisspeptin neurons and two coreleased neurotransmitters (neurokinin B and dynorphin). In this paper, the researchers used three approaches to investigate the mechanisms by which the ARN^{KISS} neuronal network operates.

First, the researchers used GCaMP miniscopes in freely moving male mice to record the activation of each kisspeptin neuron during spontaneous synchronization events. "Then, to examine the contributions of key neurotransmitters and neuropeptides coreleased by ARN^{KISS} neurons we developed a novel in vitro brain slice preparation," explains author Paul Morris. This approach enabled the researchers to maintain spontaneous synchronizations within the neural network and to assess the effects of a range of receptor antagonists. Finally, the researchers used in vivo GCaMP fibre photometry coupled with microinfusion of the receptor antagonists directly into the ARN.

"It turns out that the key transmitter enabling the synchronized activity of kisspeptin neurons is the small amino acid transmitter glutamate," explains author Su Young Han. Unlike what is predicted by the KNDy hypothesis, dynorphin controlled the frequency of glutamate-driven synchronization and neurokinin B facilitated the end-stage of synchronization. In addition, neither neurokinin B nor dynorphin were essential for ARN^{KISS} neuron synchronization.

"This study reframes a long-held hypothesis regarding the operation of a key hypothalamic central pattern generator," concludes author Allan Herbison. "The mode of synchronization within the ARN^{KISS} neural network is essential for normal fertility; we therefore expect that this significant advance in our understanding of the system will lead to future clinical treatments for infertility." The researchers also highlight several areas for future research, such as determining whether the same mechanism is present in female mice and how the synchronization is turned off.

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