Neuroendocrine
BRIEFING
61

Staccato and Legato of kisspeptin neurons driving reproduction

SUMMARY
Kisspeptin is a neuropeptide that plays a critical role in regulating reproduction by controlling a specific population of neurones that release gonadotropin-releasing hormone (GnRH). The major populations of kisspeptin neurones are located in two distinct hypothalamic nuclei. In the past decade, there have been significant advances in unraveling the roles of these two kisspeptin neurone populations as the functional control towers of GnRH surge and pulse generation, crucial mechanisms in the regulation of fertility.

BSN
British Society for Neuroendocrinology

The Kisspeptin duo

Reproduction is an essential process in species maintenance. In mammals, reproduction is controlled by an orchestrated network involving the brain, anterior pituitary gland and gonads. The hypothalamic GnRH neurones drive gonadotropin (luteinizing [LH] and follicle stimulating hormone [FSH]) secretion from the pituitary gland, either in pulsatile or prolonged-surge modes. The correct pattern of release is essential to maintain a normal reproductive cycle: LH and FSH pulses are important in stimulating follicle growth and sex steroid secretion; whereas the LH surge is a critical signal for ovulation. Kisspeptin, a neuropeptide, is the most critical upstream regulator determining GnRH neurone output. Considering the two distinct modes of GnRH and LH secretion during an ovarian cycle, it would be prudent to have separate control systems regulating these patterns. Indeed, two distinct populations of kisspeptin neurones have been identified: one in the preoptic area - the 'surge' generator, and one in the arcuate nucleus - the 'pulse' generator. Together, the kisspeptin neurone duo orchestrates the two main modes of gonadotropin secretion, maintaining fertility.

A different 'KISS' for different occasions

Although the pulse and surge generator kisspeptin neurones share a common goal – to stimulate GnRH neurones and promote GnRH secretion, they possess different morphological and neurochemical identities. For example, the surge generator population are sexually dimorphic - a dense population of kisspeptin neurones, projecting to GnRH neuronal cell bodies, is found only in females. This makes sense, as ovulation is only required in females. On the other hand, the pulse generator population is found in both males and females, and they project mainly to the distal projections of GnRH neurones near the median eminence. Moreover, the surge generator neurones in the preoptic area mainly use kisspeptin, GABA and galanin co-transmission, whereas the arcuate nucleus pulse generator population uses neurokinin-B (NKB), dynorphin, and glutamate. The different neurochemical identities between populations presumably facilitate different modes of control over GnRH secretion.

Importantly, these two populations of kisspeptin neurones are differentially regulated by changes in gonadal steroid hormones. This is key for maintaining the negative and positive feedback loops between the brain and gonads which control appropriate patterning of GnRH and gonadotropin secretion, that in turn regulate gonadal hormone secretion. Notably, KISS1 gene expression in the surge generator population is upregulated by estrogen, whereas the opposite is true for the pulse generator population. Hence, during the preovulatory phase, elevated estradiol levels enhance the activity of the surge generator kisspeptin neurones. This, in turn, facilitates sustained release of GnRH and contributes to the onset of the LH surge. Conversely, estradiol and progesterone, the two primary steroid hormones produced by the ovaries, effectively inhibit the generation of GnRH pulses. Indeed, during the period of the GnRH and LH surge, the pulse generator slows down and often halts, coinciding with elevated levels of estradiol

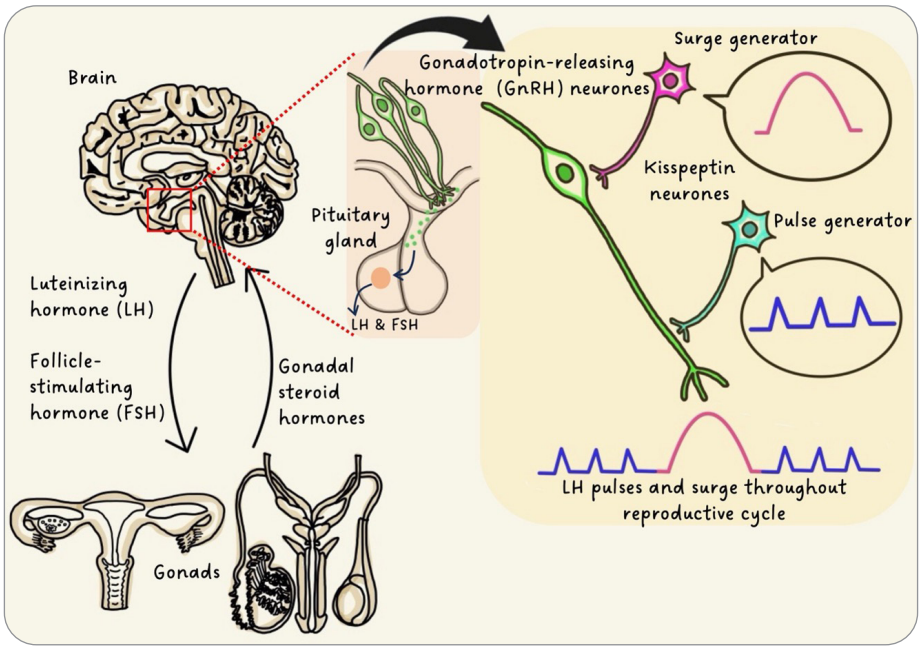

Figure: The interaction between the brain and gonads is essential for reproduction. Hypothalamic gonadotropin-releasing hormone (GnRH) neurones stimulate gonadotropin release from the anterior pituitary, with gonadal feedback regulating GnRH secretion. Kisspeptin neurones in the arcuate nucleus (blue) and preoptic area (pink) control the two primary modes of GnRH secretion: pulse and surge, respectively.

and progesterone. The precise mechanism by which varying levels of estradiol and progesterone influence kisspeptin neuronal activity and gene expression in both the surge and pulse generator remains to be elucidated. However, it is evident that the divergent effects of these steroid hormones on the two principal control centers of GnRH secretion contribute to the system's ability to efficiently transition between different operational modes throughout the reproductive cycle.

'KISS'ing Techniques

Advances in scientific techniques have enabled us to understand how kisspeptin neurones coordinate their activity to efficiently release gonadotropins. For example, optogenetics and calcium imaging techniques have revealed that the pulse generator kisspeptin neurones exhibit highly synchronised activity that faithfully drives LH pulses. The exact mechanism underlying this synchronisation is under investigation. Although species differences may exist, in mice, it seems to be built upon more localised miniature synchronisations involving fewer numbers of cells operating in a stochastic way. Glutamatergic transmission is critical for these local mini-synchronisations, where co-expressed NKB works as a potentiating mechanism and dynorphin as a brake for synchronised activity to occur.

Genetic approaches have also provided important insights into understanding how kisspeptin neurones operate. A recent transcriptomic study revealed expression of a massive number of genes in arcuate nucleus kisspeptin neurones and their responses to estrogen, including those neuropeptides required for synchronisation. The genetic knock-out or knock-down of certain genes using Cre-lox recombinase or genetic scissors such as CRISPR-Cas9 has also been illuminating. For example, transgenic knock-out or time-precise knock down of estrogen receptor alpha from the pulse or surge generator kisspeptin neurones has revealed the importance of estrogen signalling in the activity patterns of both populations, and in the maintenance of normal cyclicity.

Still learning to 'KISS'

In the last decade, huge advances have been made in our understanding of kisspeptin neurones. We have learned about the relationship between brain commands and hormone secretion, and are beginning to understand how the system is integrated. These insights are invaluable for understanding the possible mechanisms underlying reproductive disorders, such as polycystic ovarian syndrome or hypothalamic amenorrhea. Although information about the physiology of the pulse generator kisspeptin neurones has been garnered, that of the surge generator neurones have not been thoroughly addressed to date. Furthermore, the detailed neural circuitry formed by the kisspeptin neurone duo and their role in integrating reproductive biology remains to be elucidated.

Author information

Dr. Su Young Han
Department of Physiology, Development and Neuroscience,
University of Cambridge, UK
syh35@cam.ac.uk

Editor

Dr Paula Brunton
Centre for Discovery Brain Sciences
University of Edinburgh, UK
p.j.brunton@ed.ac.uk

View full Briefings series:
www.neuroendo.org.uk