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Kisspeptin is providing new insights into the control of reproduction

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Abstract – The kisspeptins are a group of recently discovered peptide hormones (collectively termed kisspeptin), which play a pivotal role in reproduction. Research investigating the actions of kisspeptin is helping to elucidate the regulatory mechanisms which govern fertility and may lead to the development of novel treatments for some reproductive disorders.

KEY WORDS: Kisspeptin, reproduction

Can you remember being taught the reproductive cycle in medical school? Essentially, in men, the pituitary gland releases luteinising hormone (LH) and follicle stimulating hormone (FSH), which stimulate testosterone production and sperm production. Testosterone and inhibin feedback negatively to the pituitary, resulting in a steady testosterone level. In women, the system of negative feedback is similar, with LH and FSH stimulating oestradiol production, and negative feedback of oestradiol to the pituitary. Progesterone is an added complication, but is more important when a woman becomes pregnant.

What was never satisfactorily explained was that at some point in the menstrual cycle, the negative feedback would be replaced by a short period of positive feedback, with big rises in both LH and oestradiol levels occurring over the course of a few days, after which negative feedback becomes the norm once again. The triggers for this change have been a mystery. An additional puzzle has been the identity of the factor that initiates the increase in the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from specialised hypothalamic neurones, which marks the onset of puberty. It now seems that kisspeptin could be the missing link that provides the answers researchers have been seeking.

Kisspeptins are a group of peptide hormones that are secreted by certain populations of neurones. They are named after Hershey's chocolate kisses rather than their role in reproduction (which may be disappointing for the romantics among you). Kisspeptins are produced from the enzymatic breakdown of the 145-amino-acid precursor product of the *KISS1* gene, but they differ in the length of their constituent amino acid chains. Each of the kisspeptin isoforms have the ability to activate the kisspeptin receptor (also known as the GPR54 receptor).[1,2] Activation of the kisspeptin receptor results in the secretion of GnRH, which in turn stimulates the release of gonadotrophins from the pituitary gland.

The kisspeptin receptor has been found in many organs in the body, including those that play vital roles in reproduction. Loss-of-function mutations in the kisspeptin gene (*KISS1*) or the kisspeptin receptor gene (*GPR54*) have been identified in adults who did not go through puberty and suffer from hypogonadotrophic hypogonadism.[3–5] Conversely, precocious puberty has been described in an 8-year-old girl with an activating mutation of the kisspeptin receptor gene (*GPR54*).[6]

The pre-ovulatory phase of the female menstrual cycle is unique in that the negative-feedback effect of oestradiol changes transiently to a positive feedback effect that produces an LH surge and subsequent ovulation. This positive feedback effect is mediated by the alpha isoform of the oestrogen receptor, which is expressed on kisspeptin neurons but not on GnRH neurons.[7]

Evidence that kisspeptin's role in reproduction is not limited to puberty but extends into adulthood continues to accumulate. Administering kisspeptin to healthy men produces a rise in LH, FSH and testosterone levels.[8] Similarly, administering kisspeptin to healthy pre-menopausal women and women with functional hypothalamic amenorrhoea (secondary to low body weight) produces elevations in their serum gonadotrophin levels.[9,10]

The kisspeptin story becomes even more interesting when prolactin-induced amenorrhoea is considered. High prolactin levels suppress GnRH pulsatility leading to amenorrhoea. Physiological hyperprolactinaemia occurs during pregnancy and lactation, and it prevents conception during these states when further offspring could jeopardise the wellbeing of existing vulnerable developing foetuses or young children who have not been weaned. Similarly, high prolactin levels that are produced by prolactin-secreting pituitary tumours are one of the most common causes of infertility. Kisspeptin neurons express prolactin receptors and kisspeptin administration has recently been demonstrated to restore GnRH pulsatility and ovulatory menstrual cycles in mice that had hyperprolactinaemia-induced amenorrhoea.[11]

Since its discovery over a decade ago, the role of kisspeptin in reproduction is becoming clearer. It is an essential mediator of normal reproduction (Fig 1). Human studies have shown that kisspeptin administration is safe and well tolerated.[8-10] Furthermore kisspeptin administration has been demonstrated to stimulate gonadotrophin and sex-hormone release in animals, healthy men, healthy women, women with hypothalamic amenorrhoea, and mice with hyperprolactinaemia-induced

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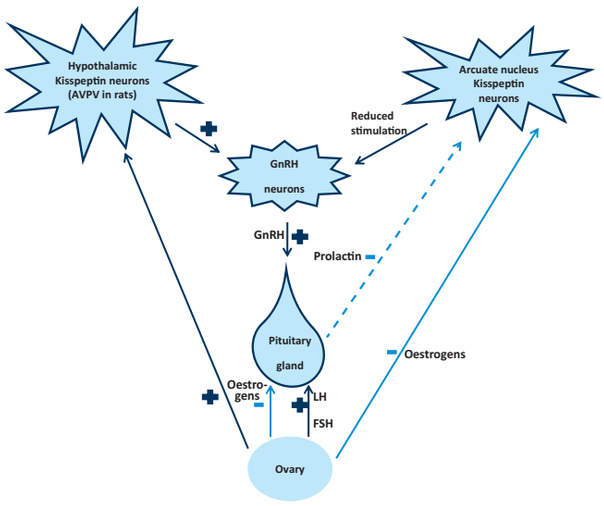

Fig 1. Hormonal interactions in a pre-menopausal woman. Oestrogens usually exert an inhibitory effect (–) on the pituitary gland and kisspeptin neurons located in the arcuate nucleus. However, in the pre-ovulatory phase of the menstrual cycle they exert a stimulatory effect (+) on other populations of kisspeptin neurons located in the hypothalamus (in the anteroventral periventricular [AVPV] nucleus in rats). Kisspeptin has a stimulatory effect on the hypothalamic GnRH neurons with consequent secretion of GnRH, which in turn results in pituitary release of LH and FSH and downstream stimulation of the ovary. Prolactin may have an inhibitory effect on kisspeptin secretion. AVPV = anteroventral periventricular; GnHR = gonadotrophin-releasing hormone; LH = luteinising hormone; FSH = follicle stimulating hormone.

amenorrhoea. Therefore, kisspeptin may become a useful addition to the treatments of patients with infertility resulting from disorders such as hyperprolactinaemia, particularly if current treatments such as dopamine agonists are poorly tolerated.

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