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Kisspeptin and its receptor: new gatekeepers of puberty

SUMMARY

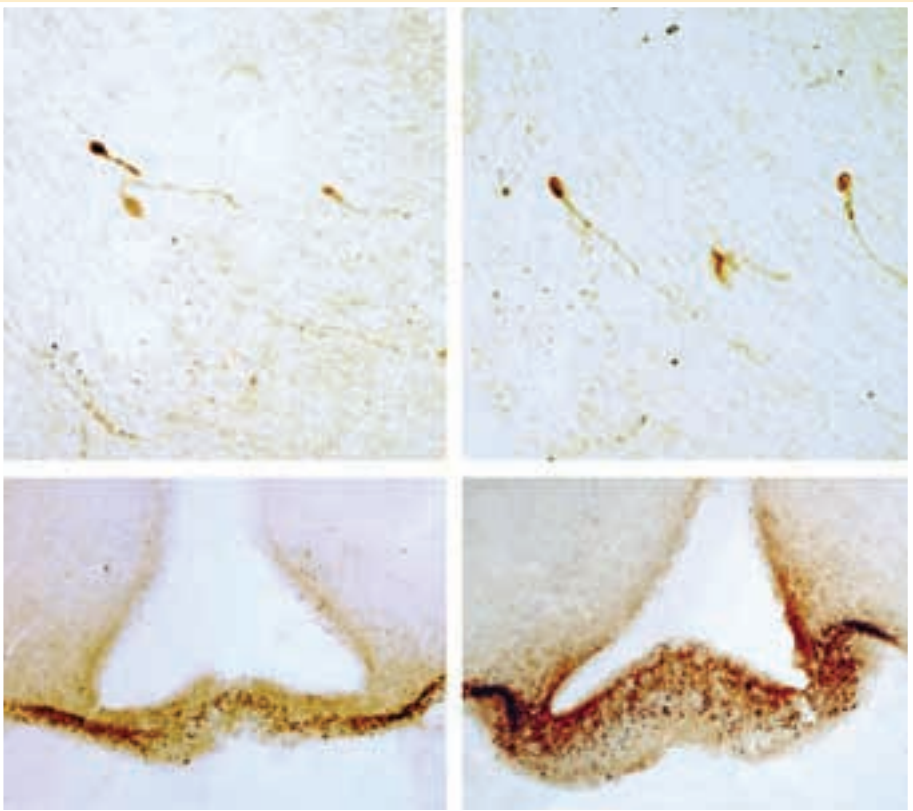
The recent finding that the hormone kisspeptin plays a pivotal role in the onset of puberty is one of the biggest discoveries in human reproductive biology in 30 years. Mutations in the receptor for kisspeptin cause humans and mice to fail to reach puberty and to be sterile. It is the first time since the identification of GnRH that a single gene is found to have such a dramatic effect on reproduction. This discovery opens new possibilities in the treatment of reproductive disorders such as delayed or advanced puberty, infertility, and sex hormone-dependent cancers.

It started with a kiss . . .

The discovery of the role of kisspeptin and its receptor, GPR54 (G-Protein Coupled Receptor 54) in puberty is the most exciting finding made in the field of reproductive biology since the discovery of Gonadotropin-releasing hormone (GnRH) in the 1970s. GnRH is the master hormone of the reproductive axis: secreted by a small group of neurons in the hypothalamus, it stimulates the pituitary gland, which in turn produces hormones called gonadotropins that stimulate the gonads (testes and ovaries), making them mature and produce sperm or eggs. Activated transiently during the first months of postnatal life, the GnRH system remains dormant until its reactivation signals the onset of puberty. Since the discovery of GnRH, many new hormones have been shown to play a role in reproduction, but none of them has such a dramatic effect as kisspeptin.

A hormone comes of age

Discovered in the late 1990s, kisspeptin was first given the name metastin, because it was thought to play a role in tumor metastasis (the



The anatomy and localisation of GnRH neurons (intense brown colour) is identical in GPR54 knock-out (right) and normal mice (left).

invasion of cancer cells through the body). However, in 2003, three groups identified the role of the kisspeptin receptor (GPR54) in reproduction. Our group at Paradigm Therapeutics did so by engineering a mouse that lacks the GPR54 gene – a technique known as 'knock-out' (which we use to discover the function of novel genes, to develop new drugs). Two other groups, one led by Nicolas De Roux in Paris, and the other by Bill Crowley in Boston, validated these observations in humans by identifying inbred human families with mutations in the GPR54 gene. When GPR54 is absent or mutated, mice and humans do not undergo puberty, their gonads are small, their sex hormone (estrogens and testosterone) and gonadotropin levels are low, and they are sterile. Interestingly, this can be reversed with hormonal treatment, and humans with mutations of GPR54 have gone on to have healthy children. This shows that whilst the hormone kisspeptin is essential for puberty to occur, its absence does not cause any developmental defect in the reproductive organs, and that the gonads and pituitary gland are still able to respond to stimulation even when the age of puberty has passed.

In mice that lack GPR54 the anatomy and localisation of GnRH neurons is unremarkable (see figure), and similarly the amount of GnRH in the brain is not different from that of normal mice. This suggests that there is no defect in the actual synthesis of GnRH, but that somehow, its release from the brain is impaired, and therefore it can not stimulate the pituitary gland adequately.

What a little kiss can do . . .

Kisspeptin is a small peptide produced by a gene called kiss-1. Since the discovery of the role of GPR54 in 2003, this new field of research has literally exploded, and aside from the three original research groups, many other scientists across the world have focused on trying to unravel the mechanism of action of kisspeptin. In several animal models, a single injection of kisspeptin stimulates a massive increase in the secretion of gonadotropins, as strong as that observed by administering GnRH itself. Repeated injections in immature rats can advance the age of puberty. We have been able to show that GPR54 is expressed by GnRH neurons and that kisspeptin directly stimulates the release of GnRH.

". . . humans with mutations of GPR54 have gone on to have healthy children"

Very recently, a group of Japanese scientists delivered an antibody directed against kisspeptin into the brain of female rats and this stopped their reproductive cycle. This demonstrates that inhibiting the effect of kisspeptin, even once puberty has occurred, still blocks reproductive function, and that the secretion of kisspeptin is necessary not only for puberty to occur, but also for reproductive function to continue. Another group of scientists in Spain found that administering kisspeptin in food-restricted rats still stimulates the release of gonadotropins. This is a fascinating observation, demonstrating the power of kisspeptin on the reproductive system because in food deprived conditions the reproductive system of most mammals becomes dormant.

One area that has been the object of particular interest, is the identification of the neurons that secrete kisspeptin. They are found mostly in a small area of the hypothalamus called the arcuate nucleus, and they seem to make contact with GnRH neurons, which are located in another area of the hypothalamus. However, as yet the exact mechanism of action through which they stimulate the GnRH neurons is unknown, and naturally the most important question to answer next is: what controls the release of kisspeptin itself?

The discovery of the role of kisspeptin and GPR54 opens exciting new possibilities in the treatment of a variety of conditions including delayed or advanced puberty, infertility, and also for the treatment of sex hormone-dependent cancers such as prostate cancer.

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