Neuro-endocrinology

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BRIEFINGS

Is love possible without *Kiss1*-es?

SUMMARY

The hypothalamic kisspeptins and their receptors are potent regulators of the gonadotropic axis through the control of GnRH neuronal activity. But there is another population of kisspeptin neurons in the amygdala, a brain area that integrates odour, visual and auditory information, and which has a key role in social behaviours.

Kisspeptins are a family of proteins that are essential for reproduction. The kisspeptin gene was discovered in 1996 by a group working in Hershey, Pennsylvania. It is named after the city's chocolate 'Kisses'.

The critical function for the perpetuation of the species is reproduction, and this is controlled by a complex network of signals that operate at the *hypothalamic-pituitary-gonadal axis*. Correct functioning of this network relies on interactions between the hypothalamus, where a subset of neurons synthesizes gonadotropin-releasing hormone (GnRH); the anterior pituitary, which secretes gonadotropins (luteinizing hormone and follicle stimulating hormone); and the gonads, which release sex steroids (testosterone and estradiol). Hypothalamic GnRH neurons, at the top of this hormonal cascade, integrate a wide array of incoming signals, including other neuropeptides, neurotransmitters and peripheral factors (including metabolic signals). However, and excitingly for the field, new potent regulatory factors have been identified; most prominently, kisspeptin has been identified as a potent regulator of the gonadotropic axis.

Kisspeptin background

Kisspeptins comprise a family of neuropeptides encoded by the *Kiss1* gene, and they act via a cell membrane-bound receptor called *Kiss1r*. Kisspeptin signalling was first seen to be essential for reproductive function when humans suffering a pathological condition of infertility called *hypogonadotropic hypogonadism* were found to harbour inactivating mutations in the kisspeptin receptor gene. Transgenic mice engineered to lack the kisspeptin receptor (*Kiss1r* KO), or the kisspeptin gene (*Kiss1* KO) were then shown to be a complete phenocopy of their humans equivalents. The kisspeptin

Image courtesy of Hershey Community Archives, Hershey, PA

receptor is expressed in most GnRH neurons, and kisspeptin administration strongly stimulates gonadotropin secretion, so it was soon established that kisspeptin is a major regulator of GnRH/gonadotropin secretion, and hence a key determinant of sex steroid production and secretion by the gonads.

Where are the kisspeptin neurons?

Kisspeptin neurons have been most thoroughly studied in rodents. These neurons are located in two nuclei in the hypothalamus, the *arcuate nucleus* and the *anteroventral periventricular nucleus*. These two populations mediate negative and positive feedback respectively from circulating sex steroids onto GnRH neurons. But, for fully functional reproduction, the endocrine hormonal milieu must be co-regulated with an appropriate social behaviour (e.g. discriminating between receptive females and aggressive males), and interestingly, kisspeptin neurons may be involved in this by a *third* population of kisspeptin neurons, located in the amygdala.

The Amygdala

The amygdala is responsible for complex social behaviours including affiliation, social cognition, aggression and anxiety/stress responses. In fulfilling this role, it must integrate a wide range of odour, visual and auditory information that identify particular individuals and their social relevance. This information is key to allow an animal to express relevant and effective sexual behaviours.

Pheromones, *Kiss1*-es and sex "appetite" (libido)

Most mammals recognize other individuals by smell. The idea that the olfactory bulb is relevant for social behaviours in humans, at least consciously, is not widely accepted because the olfactory bulb in humans is much smaller than in other mammals. The olfactory bulb in rodents is organised into the *main olfactory system* and the *vomeronasal* or *accessory olfactory system*. The vomeronasal olfactory system processes pheromone information, and comprises the *vomeronasal organ,* located in the nasal cavity, and the *accessory olfactory bulb* in the posterior-dorsal area of the olfactory bulb. Mitral cells in both the main and the accessory olfactory system send processed odour information to diverse brain sites via axons that leave the olfactory bulb in the lateral olfactory tract. Mitral cells in the accessory olfactory bulb project to the *vomeronasal amygdala,* and interestingly, this is where the amygdala kisspeptin neurones are located.

"fully functional reproduction must be co-regulated with appropriate social behaviour"

The connection between the accessory olfactory bulb and the amygdala kisspeptin population might explain several biological phenomena where an odour stimulus and a hormonal dependent-behaviour response (acute or chronic) are correlated. These phenomena include the *Coolidge effect,* where a male apparently exhausted after breeding with several females finds a renewed sexual "appetite" (libido) when a novel female is introduced in the cage; the *Whitten effect*, where groups of females start to cycling in synchrony when exposed to a male or his odor; the *Bruce effect* where implantation failure occurs in a recently mated female mouse when exposed to a novel male; and the *Vandenbergh effect* which describes an advance in the onset of puberty in female mice exposed to male odour. These effects indicate that exposure to pheromones/odour cues can fundamentally re-organize the gonadotropic axis, and the amygdala kisspeptin neurons might have a major role in this.

Love starts with a *Kiss1*

Are amygdala kisspeptin neurons implicated in the process of social attachment? It is worth speculating that, working together, affiliation and aggression are both critical for perpetuation of the species. Aggression allows better access to resources, while affiliative interactions are necessary for reproduction; both behaviours are modulated by testosterone. The amygdala kisspeptin neurones are directly sensitive to testosterone and kisspeptin controls its production and secretion.

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