New brain hormone

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Nightshift workers to reset their biological clock (so that they are alert at night) and long airline flight travellers to prevent jetlag pop melatonin pills. They should be cautious about taking popular supplement melatonin, say discoverer of new brain hormone.

Japanese and University of California, Berkeley researchers have discovered a new actor in the vertebrate (avian and mammalian) reproductive system, a hormone that fills a role long suspected, but undetected until now. The new study shows that melatonin, a hormone available without prescription, has broader effects in the brain than once thought. In experiments on birds[1–3] and mammals[4], the researchers found that melatonin switches on a recently discovered hormone called gonadotropin-inhibitory hormone (GnIH), which has been found to have the opposite effect to the key hormone priming the body for sex – gonadotropin-releasing hormone (GnRH). In birds and mammals, switching off GnRH causes the gonads (testes and ovary) to shrink and be inactive.

The newly discovered hormone GnIH is a small protein, or peptide. It puts the brakes on reproduction by directly inhibiting the action of the central hormone of the reproductive system – GnRH. This hormone stimulates the pituitary gland to activate the reproductive system, whereas GnIH appears to reduce the effects of GnRH stimulation (Figure 1).

The discovery in bird (Japanese quail) and mammal (Hamsters) of this new system for regulating reproduction strongly suggests that the hormone plays a similar role in the reproductive systems of humans and other mammals. The human genome, in fact, contains a gene for GnIH. If the new finding is mirrored in humans and other mammals, it would offer physicians another means of tweaking the reproductive system to fix problems ranging from infertility to precocious puberty, and also provide animal breeders with a new way to manipulate the productivity of livestock. The human reproductive system is regulated like a thermostat, with a number of hormones and factors produced along the 'reproductive axis' acting via feedback loops to keep the body's hormones within the optimal range for fertility and successful mating. The head of the axis is the brain's hypothalamus producing GnRH, which communicates via a blood portal with the anterior pituitary and stimulates production of the hormones gonadotropin, luteinizing hormone and follicle-stimulating hormone. These hormones are dumped into the bloodstream and make their way to the gonads, where in males they stimulate production of testosterone and the maturation of sperm. In females, the hormones stimulate production of oestradiol, a sex-steroid hormone and the body's main form of oestrogen, and regulate ovulation, the production of fertile eggs (Figure 1).

Oestradiol and testosterone, in turn, feedback on the pituitary to shut down production of pituitary hormones, establishing feedback that keeps the body's sex hormones on an even keel. Oestradiol also works higher in the brain, on the hypothalamus, to ramp down production of GnRH, but how this works has been a relative mystery. The new study provides an answer: Oestradiol stimulates cells in the dorsomedial nucleus of the hypothalamus to produce GnIH, which appears to act directly on cells in the hypothalamus to turn off their production of GnRH.

Researchers have long sought inhibitors of pituitary gonadotropins, but many had come to believe that such a direct inhibitor was unlikely in the complex cast of hormones and factors in the reproductive system. The inhibiting or braking hormone may complement the 'gas pedal' role played by another recently discovered hormone, kisspeptin, that stimulates GnRH[5].

Lance Kriegsfeld (UC Berkeley, Department of Psychology) said, now we have a novel neural pathway mediating the regulatory actions of sex steroids. This is an example of the reproductive system being fine-tuned, said George Bentley (UC Berkeley, Department of Integrative Biology). 'We know a lot about the gross regulation of the reproductive system, but fine tuning has not been well understood at all[6].

GnIH was discovered in quail by Japanese researchers led by Kazuyoshi Tsutsui (Faculty of Integrated Arts and Sciences at Hiroshima University). The discovery supplied one of the last remaining pieces of the bird's hormone system that controls reproduction. GnIH seemed to be the missing antagonist that switches off pituitary gonadotropins, and work by Tsutsui and Bentley in quail and white-crowned sparrows confirmed its role in turning down production of GnRH and thus switching off the gonads. While Bentley collaborated with Tsutsui to determine how GnIH works in birds, the two also teamed up with Kriegsfeld to explore the implications in mammals. Kriegsfeld began collaborating with the group working with Rae Silver, a Kaplan Professor of Natural and Physical Sciences at Barnard College, and continued this research in his own lab. Using fluorescent antibodies to GnIH, they were able to locate where

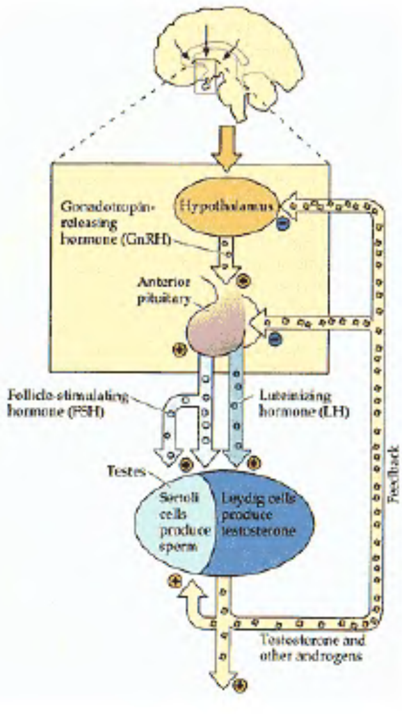

Figure 1. Hormonal regulation of male reproductive system (similar in female), involves many feedback loops that regulate fertility. The newly discovered hormone, gonadotropin-inhibitory hormone (GnIH), appears to be produced by the hypothalamus, where it seems to inhibit the production of gonadotropin-releasing hormone (GnRH), thereby putting a brake on reproduction at the very top of the reproductive axis (reproduced from ref. 5).

in the brain the hormone is made: in the nerves of the dorsomedial hypothalamus. The axons of these nerves project to numerous areas of the brain where nerve cells produce GnRH, and staining showed that these axons contacted GnRH-producing cells, suggesting direct effects. They showed that as in birds, GnIH also rapidly inhibits production of luteinizing hormone by the pituitary. Along with the fact that the cells containing GnIH also have receptors for oestrogen-like compounds such as oestradiol, the combined evidence suggests that GnIH is a direct inhibitor of GnRH. Because the brain cells producing and secreting GnIH send their axons into many areas of the brain, GnIH may have other effects on the brain, too. Though we do not know in mammals where the receptors are for GnIH, it looks like the hormone produces multiple effects in the brain. In birds, the hormone not only affects reproductive hormones, but also sexual behaviour in females, such as readiness to copulate. Interestingly, the neurons producing GnIH are in an area of the brain, the dorsomedial nucleus of the hypothalamus, that coordinates and integrates information from external stimuli, the senses and from motivational and emotional inputs.

Kriegsfeld and Bentley along with Takayoshi Ubuka, Kazuhiko Inoue and Kazuyoshi Ukena plan to continue their investigation of the role of GnIH in birds and mammals.

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Fungal farming: A story of four partner evolution

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Agriculture or farming can be loosely defined as the science and art of growing one's own food. It is a science that humans have evolved some 10,000 years ago; however, a group of ants could be the first ones to invent this practice ~50 million years ago. Over time, they have perfected the technique of propagating fungi that serve as food in specialized fungal farms and keeping this farm free from any disease. There is an interesting quadripartite association between the ant, fungus, fungal parasite and antibiotic-producing bacterium, which we are beginning to understand only recently[1].

Attine ants are found mostly in North America and comprise 200 described species in 12 genera that are obligatorily dependent on fungiculture for food. Although attines derived from a single ancestor extant species, cultivate multiple and phylogenetically distant lineages of fungi, most of these fungi belong to the family Lepiotaceae (Agaricales: Basidiomycota). Fungal cultivars, serving as the primary food source for the ants, are carefully manured by the ants with plant substrate, insect frass or seeds. Foundress queens propagate the fungus clonally, by carrying inocula in their mouths during their nuptial flight to establish new colonies and farms. Although at least some 'lower' attines (phylogenetically basal lineages) propagate cultivars that were recently domesticated from free-living populations of Lepiotaceae, the 'higher' attines (a derived monophyletic clade that includes the leaf-cutting ants) are thought to propagate ancient clones, likely several million years old. Among the attines, the two genera of leaf-cutting ants, namely *Acromyrmex* and *Atta* exhibit the most complex fungicultural systems. Colonies of *Atta* spp. can survive for extended periods, often living for 8–10 years or more after initial nest-founding. Foundress queens of these species establish new colonies by digging chambers in the soil, expelling the fungal pellet that they bring from their natal nest, and initiating the cultivation of their own gardens, started using faecal material provided by the queen. Nest-founding occurs within a claustral chamber that remains closed until the first brood is reared, at which point the new workers begin foraging for leaf material outside the initial chamber. Fungus-growing ants are thought to be capable of cultivating their fungus in axenic (single species) 'monocultures', despite continuous exposure to the competitively advantaged microbes already present in the vegetative material that is added to the garden. It also appears that the fungi cultivated by these higher attines are ancient clones that have been evolving strictly within this mutualism for millions of years. On the other hand, in the lower attines there is vertical transmission of the fungus from parent to offspring colony, with occasional horizontal (lateral) transfers of cultivars between ant colonies and perhaps domestication of novel cultivars.

It was initially thought that these gardens are maintained as monocultures despite continuous exposure to the competitively advantaged microbes already present in the vegetative material that is added to the garden. Currie *et al.*[2] conducted the first extensive study of nonmutualistic filamentous fungi associated with fungus-growing ant gardens and found that fungi in the hyphomycete genus *Escovopsis* (anamorph allied with Hypocreales: Ascomycota) were the most common nonmutualistic ones present. *Escovopsis* can have a dramatic impact on the health and survivorship of fungus-growing ant gardens. As previously noted, *Escovopsis* can rapidly overgrow gardens in the absence of