

# Sexual Responses Are—Almost—All in the Brain

*The brain regulates most aspects of reproductive life, from the development of the sex organs to their ultimate aging*

HUMAN SEXUAL RESPONSES may not all be in the brain, but a good part of them are. Not only do the sex hormones modify brain structure and function, but the brain in turn influences the development, activity, and ultimate aging of the male and female sex organs. As Roger Gorski of the University of California School of Medicine in Los Angeles points out, "The brain is also part of the reproductive system."

First and foremost among the ways in which the brain influences reproduction is by producing gonadotropin-releasing hormone (GnRH). This hormone, which also goes by the name luteinizing hormone-releasing hormone (LHRH), is a ten-amino acid peptide that is secreted by nerve cells in a portion of the brain called the hypothalamus. GnRH is receiving a great deal of attention—more than one-third of the presentations at this year's Galveston Neuroscience Symposium\* dealt with it—because it plays a critical role in establishing and maintaining normal reproductive activities.

The work has clinical implications. Disruption of normal GnRH release patterns can lead to infertility in both women and men. For example, women who exercise strenuously, such as ballerinas and serious runners or gymnasts, often stop ovulating and menstruating. Recent research indicates that this is the result of a decline in their GnRH production.

Moreover, contrary to previous thinking that menopause is caused solely by a depletion of eggs in the ovary, the indications now are that alterations in GnRH release patterns and decreased responsiveness to the hormone also contribute to the onset of the menopause.

GnRH is needed for normal reproduction because it stimulates the release of the gonadotropins, luteinizing hormone and follicle-stimulating hormone, from the pituitary. The gonadotropins in turn regulate the production of the sex hormones by the ovary and testes, and thereby also regulate sperm production and ovulation.

One of the most straightforward demon-

strations of the necessity of GnRH for reproduction came about 2 years ago. A group of investigators, including Anthony Mason of Genentech, Inc., in South San Francisco, found that hereditary hypogonadism in the mouse is caused by a mutation that removes part of the GnRH gene. Animals with the mutation have underdeveloped gonads, are sterile, and do not mate normally.

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The investigators also showed that introduction of the normal GnRH gene into the genome of hypogonadal mice cured the animals of the defect, allowing them to mate and produce offspring. "Mammalian reproduction seems to be completely dependent on the activity of this gene," say Karoly Nikolics, a member of the Genentech group.

The GnRH gene must be turned on at the beginning of puberty, apparently as a result of some change in the brain itself. "It's clear now that the onset of puberty is a brain-driven event. It is initiated even in the absence of gonads," says Sergio Ojeda of the Oregon Regional Primate Research Center in Beaverton. Children who are born without gonads, for example, begin making the gonadotropins at the normal time.

According to Ojeda, the lack of GnRH secretion before puberty in female rats is not due to an intrinsic inability of the hypothalamus to synthesize the hormone. It will do so well before puberty if stimulated by treatment with a prostaglandin. "There is no doubt that the system can operate early in development and is capable of maintaining a pulsatile release of LHRH," Ojeda asserts. Other researchers have found that GnRH must be released in pulses occurring approximately every 30 minutes in the rat or every 1 to 3 hours in the human in order to stimulate gonadotropin secretion.

Ojeda hypothesizes that the hypothalamic

neurons fail to secrete GnRH before puberty, even though they have the capacity to do so, because they do not receive the incoming neuronal signals that are needed to trigger secretion. This may be because the necessary neuronal connections are not in place before the onset of puberty.

Ojeda and his colleagues have evidence indicating that growth factors, such as nerve growth factor and basic fibroblast growth factor, may participate in the establishment of those connections. They find, for example, that basic fibroblast growth factor induces the differentiation of GnRH-producing nerve cells that are maintained in culture. Under the growth factor's influence, the cells send out projections, called neurites, and form connections with one another.

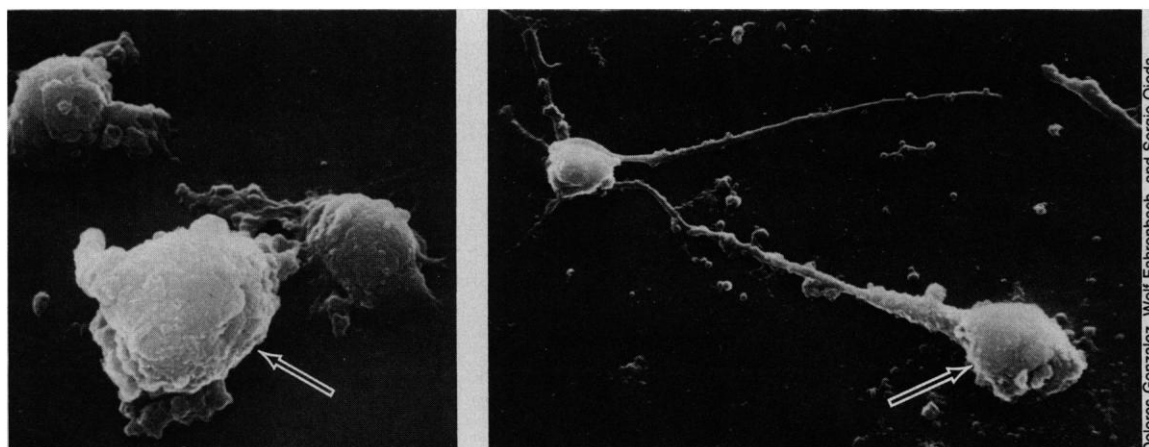
Menopause, as well as puberty, may begin with changes in the brain and pituitary gland, not the ovary. Experiments conducted in Terry Parkening's laboratory at the University of Texas Medical Branch at Galveston have shown that young mice whose ovaries are replaced with ovaries taken from aged animals that are no longer capable of reproducing can mate and produce baby mice. "The aged ovary placed in a proper environment is still capable of responding," Parkening says. Old animals that are given young ovaries remain reproductively deficient, however.

This finding contrasts with previous views of the cause of menopause. "It was thought that exhaustion of the [ovarian egg] follicles caused the loss of reproductive ability," says Phyllis Wise of the University of Maryland School of Medicine in Baltimore. "But hypothalamic function changes in middle age and this may play an important role in the loss of fertility and cyclicity." Wise notes that the loss of follicles accelerates in women between the ages of 40 and 50, perhaps as a consequence of hypothalamic changes.

Determining which of the changes seen at the onset of menopause are primary and which are secondary is difficult, however. Maintenance of menstrual cycles depends on a network of hormonal communications between the hypothalamus, the pituitary, and the ovary that is nothing if not complex.

Not only do the gonadotropins control the production of the ovarian hormones, for example, but researchers, including Gwen Childs of the University of Texas Medical Branch at Galveston, John Marshall of the University of Michigan Medical Center in Ann Arbor, and Kevin Catt of the National Institute of Child Health and Human Development (NICHD) in Bethesda, Maryland, have shown that the ovarian hormone estradiol can make the gonadotropin-pro-

\*The symposium, entitled "Neuroendocrine Modulation of Central Nervous System Function," was held in Galveston, Texas, on 10 to 13 May.



**GnRH-producing neurons.** In the scanning electron micrograph to the left, an untreated GnRH neuron (arrow) remains undifferentiated. After treatment with basic fibroblast growth factor (right) the neurons differentiate and extend projections to one another.

Dolores Gonzalez, Wolf Fahrenbach, and Sergio Ojeda

ducing cells of the pituitary more sensitive to GnRH by increasing the number of GnRH receptors on the cells. This contributes to the big surge in luteinizing hormone secretion that is the immediate trigger for ovulation.

The sex steroids also may act on the brain to influence GnRH release, but these activities, notes William Crowley of the University of Tennessee Center of Health Sciences, are largely indirect. The effects of the ovarian hormones on LHRH secretion vary. Early in the menstrual or estrous cycle they are inhibitory. They then become stimulatory, causing a surge in GnRH that is reflected in the consequent surge of luteinizing hormone secretion by the pituitary.

After ovulation, the ovarian hormones become inhibitory again. "That's part of the fascination of the problem," Crowley says. "You have to be able to explain how ovarian hormones can convert from inhibitory to stimulatory, and back to inhibitory again."

That explanation is not yet in, but it is known that many of estrogen's effects on GnRH secretion are mediated through neurons that use the neurotransmitters norepinephrine, epinephrine, or serotonin for conveying signals to other nerve cells. Wise finds that the daily production patterns of both norepinephrine and serotonin, as well as their responses to the estrogen estradiol, become disturbed in the aging animal. Such changes might disrupt GnRH secretion.

In addition, Joan Lakoski of the University of Texas Medical Branch at Galveston has observed that the serotonin-producing neurons of the dorsal raphe nucleus, an area in the brainstem, show a decreased rate of spontaneous firing in aging rats. The nerve cells in question provide 80% of the serotonergic input to the hypothalamus and their decline in activity might be related to a decline in hypothalamic function. In addition, the pituitary's responses to GnRH may also be disturbed in the aging organism.

Somewhat surprisingly, the results of the Wise group indicate that estrogens may

bring about the brain and pituitary changes that result in cessation of female reproductive cyclicity. "Middle-aged animals that have been deprived of estrogen," Wise says, "are more like their young counterparts than other middle-aged animals." How estrogens might alter hypothalamic and pituitary function during aging is as yet not known.

Wise notes, however, that progesterone tends to counteract the effects of the estrogens in this as in other regards. Women who are taking birth control pills, therefore, need not be concerned that they are running the risk of accelerated aging, as long as the pills contain progesterone as well as estrogen, which almost all do today.

The inhibition by progesterone of GnRH release during the estrous or menstrual cycle is mediated by neurons that use opioid peptides for signal transmission. Heavy exercise may have an effect similar to that of progesterone in its inhibitory phase. Exercise causes a rise in the concentrations of the endogenous brain opiates. This may, by inhibiting GnRH release, cause the stoppage in menstrual cycles seen in women who exercise a great deal.

Although about 70% of the women who cut back on their exercise resume normal menstrual cycling spontaneously, the other 30% do not. Marshall and his colleagues have been investigating whether administration of drugs that antagonize opiate action can restore GnRH secretion and menstruation in this latter group of women. They have found that the opiate antagonist naloxone restores normal luteinizing hormone release, which indicates that GnRH release is also normal, in 65% of the women.

Naloxone needs to be administered intravenously, however, and is therefore not practical for long-term therapeutic use. The Michigan workers are currently looking at naltrexone, an opiate antagonist that can be taken by mouth, to see if it will restore ovulation. According to Marshall, the early results are mixed. Two of the five women treated thus far with oral naltrex-

one ovulated, but the others did not.

In addition to affecting mating behavior indirectly by virtue of its effects on gonadotropin release and thus on sex hormone production, the GnRH molecule, or at least a portion of it, may also have direct effects on mating, according to data presented at the neuroscience symposium by Robert Moss of the University of Texas Southwestern Medical Center at Dallas. The Moss group has shown that a fragment of the GnRH molecule containing amino acids 6 to 10 has this behavioral activity, although it is not active in releasing luteinizing hormone. Moreover, the brain contains enzymes that can split this fragment from the ten-amino acid GnRH molecule. Having two or more neuroactive peptides contained within a larger protein is a common situation.

In fact, the GnRH molecule is itself synthesized as part of a larger peptide from which it must be split, according to Nikolics. The other product released from the GnRH precursor is known as the GnRH-associated protein (GAP). The physiological role of GAP remains unclear. Nikolics has shown, however, that GAP inhibits the release of the pituitary hormone prolactin, when the production of that hormone is elevated. Prolactin is best known as a stimulator of lactation but is also produced in times of stress.

The effects of GnRH in the pituitary include stimulation of both gonadotropin synthesis and release. How GnRH produces its effects in the pituitary and the brain is currently an active area of investigation. Work by Catt at NICHD and by P. Michael Conn of the University of Iowa College of Medicine in Iowa City has shown that the hormone works through the polyphosphoinositide system for transmitting signals to the cell interior, although the details of the operation of this system are still being clarified. But no matter how GnRH produces its effects on gonadotropin secretion, its central role in regulating reproductive activity is clear. ■ **JEAN L. MARX**