

Neuro-endocrinology

BRIEFINGS

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SUMMARY

Female reproductive function is controlled by complex interactions of the brain, pituitary gland and ovary. Each of these organs produces unique hormones, and each hormone acts upon the other organs to affect a response. Differentiating the causes and the consequences of reproductive senescence in mammals is thus a “chicken and egg” puzzle. Surprisingly, recent evidence indicates a more important role for the brain in the initiation and transition to reproductive senescence.

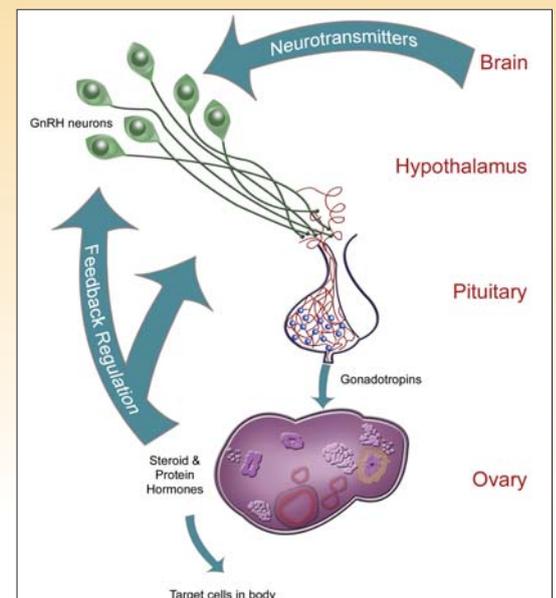
IS REPRODUCTIVE AGEING CONTROLLED BY THE BRAIN?

The process of reproductive ageing

Menopause is an inevitable consequence of the ageing process in women. Despite its occurrence in half the human population, the biological mechanisms controlling this process are poorly understood. There is no question that changes to the ageing ovary, specifically the loss of ovarian follicles, are the hallmark of menopause. Why do follicles undergo an exponential loss and an eventual depletion in middle-aged women? Part of this timing may be attributable to an intrinsic ovarian alarm clock, scheduled to go off at approximately age fifty. However, other mechanisms may be involved. The ovary is only one of the three levels of the reproductive system of mammals. Reproductive function begins with a signal produced by nerve cells in a region at the base of the brain called the hypothalamus. A group of hypothalamic neurons synthesizes a peptide hormone called gonadotrophin-releasing hormone (GnRH), and

secretes it into a capillary system leading to the pituitary gland. There, the GnRH peptide stimulates a subset of pituitary cells to release their hormones, collectively called the gonadotrophins. The gonadotrophins travel through the circulatory system to act upon the ovary, stimulating reproductive processes such as the synthesis and release of sex steroid hormones, menstrual cycles, follicular development, and ovulation. All three levels of the reproductive system, hypothalamus, pituitary, and ovary, must function in perfect synchrony for reproductive processes to occur normally. During ageing, each of these levels changes, to result in a loss of reproductive function.

Two additional regulatory processes contribute to normal reproduction and these in turn may undergo age-associated alterations. First, ovarian steroid hormones,



The many levels of the body involved in the control of reproduction are depicted schematically. Not only does hypothalamic-pituitary-gonadal function change with ageing, but feedback of ovarian hormones, and neurotransmitters in the brain that regulate GnRH neurons, also undergo age-associated functional changes. Together, this complex network controls reproduction across the life cycle, and ageing of this network results in the loss of reproductive capacity.

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particularly estrogens and progesterone, and ovarian protein hormones such as inhibin, exert complex feedback regulation upon hypothalamic GnRH and/or pituitary gonadotrophin release. Any changes in the synthesis, secretion, transport or binding of these ovarian hormones to their receptors, or alterations in receptor numbers, location and function, may modulate reproductive processes. Second, further control occurs in the hypothalamus through a complex network of neural circuits that regulate GnRH neurons. A number of central neurotransmitters and neurotrophic factors, including (but not limited to) glutamate, GABA, and norepinephrine, regulate GnRH cells differentially in aged versus young animals. Thus, during ageing, there are many potential sites that may contribute to reproductive senescence.

Role playing: the brain

The human perception that our brains don't work as well in middle age as in youth reflects normal age-related declines in neural functions controlling cognition, learning and memory. What does this have to do with reproductive ageing? It turns out that the same neurotransmitters responsible for controlling cognitive processes in brain regions such as hippocampus and cortex are part of the neural circuitry that regulates the hypothalamic GnRH neurons that drive reproduction. Moreover, these neurotransmitter systems can co-express the estrogen receptor that mediates feedback of estrogens on the brain. Thus, the central neural circuitry involved in the control of GnRH release is estrogen-sensitive, and changes in the numbers or properties of these receptors during

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ageing can modify GnRH function. Whether or not age-related changes in hypothalamic neurotransmitters controlling GnRH release cause or contribute to the loss of reproductive function is still debatable, and probably varies between species, but there is no question that the responsiveness of GnRH cells to these neural inputs undergoes age-related decline.

Role playing: the consequences

The combined loss of hypothalamic, pituitary and ovarian functions and responsiveness causes an eventual transition to reproductive failure at middle age. A biologically relevant outcome of this process is a large decline in circulating steroid hormone concentrations, back to prepubertal levels. The loss of estrogens may result in osteoporosis, hot flashes, vaginal dryness, and cardiovascular changes. From a neurobiologic perspective, estrogen deprivation has significant effects on the brain, not only on the hypothalamic circuitry controlling reproduction, but also on non-reproductive processes including cognitive functions and psychological status. These effects are explained by the widespread distribution of estrogen receptors throughout the brain.

Currently, estrogen treatment is the only effective therapy for many symptoms associated with menopause. The timing and duration of estrogen deprivation are key considerations for

deciding when, or whether, to initiate estrogen therapy for postmenopausal symptoms. Recent studies in humans have identified the perimenopause, the life stage during which the female transitions to a postmenopausal state, as a critical window determining the success of interventions. Research on animal models supports the importance of treating with hormones at a relatively short duration after deprivation, and emphasizes the need for using physiologically relevant hormones such as natural estrogens and progestins. Results of these studies are encouraging, demonstrating improvements in age-related neural functions such as cognitive decline, mood disorders, and hot flashes. Thus, understanding the role of the brain in reproductive ageing is key to improving the quality of life in a demographic group destined to live long beyond the menopausal transition.

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