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The aging reproductive neuroendocrine axis

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Abstract

It is well known that the reproductive system is one of the first biological systems to show age-related decline. While depletion of ovarian follicles clearly relates to the end of reproductive function in females, evidence is accumulating that a hypothalamic defect is critical in the transition from cyclicity to acyclicity. This minireview attempts to present a concise review on aging of the female reproductive neuroendocrine axis and provide thought-provoking analysis and insights into potential future directions for this field. Evidence will be reviewed, which shows that a defect in pulsatile and surge gonadotropin hormone-releasing hormone (GnRH) secretion exists in normal cycling middle-aged female rats, which is thought to explain the significantly attenuated pulsatile and surge luteinizing hormone (LH) secretion at middle-age. Evidence is also presented, which supports the age-related defect in GnRH secretion as being due to a reduced *activation* of GnRH neurons. Along these lines, stimulation of GnRH secretion by the major excitatory transmitter glutamate is shown to be significantly attenuated in middle-aged proestrous rats. Corresponding age-related defects in other major excitatory regulatory factors, such as catecholamines, neuropeptide Y, and astrocytes, have also been demonstrated. Age-related changes in hypothalamic concentrations of neurotransmitter receptors, steroid receptors, and circulating steroid hormone levels are also reviewed, and discussion is presented on the complex interrelationships of the hypothalamus–pituitary–ovarian (HPO) axis during aging, with attention to how a defect in one level of the axis can induce defects in other levels, and thereby potentiate the dysfunction of the entire HPO axis.

Keywords: Aging; Hypothalamus; Reproduction; Gonadotropin hormone-releasing hormone; Neuroendocrine; Pituitary; Steroid; Estrogen; Progesterone; Luteinizing hormone; Follicle-stimulating hormone; Ovulation; Estrous cycle

1. Introduction

The reproductive system is one of the first systems to show age-related decline in function, with failing reproductive function in females evident in most species long before the end of the life span. Female rats and mice have an expected life span of 2–3 years, but exhibit an increasing frequency of irregular reproductive cycles by the time of middle age (8–12 months) and become acyclic, when they are old (17–21 months) [1–3]. Similarly, fertility in women declines during the fourth decade of life, with the average age of menopause being 50–51 years. The period just prior to, during and after menopause is associated with marked hormonal changes [4–6] for review. While the life span of human females has been extended significantly in the last century, the age of menopause has remained quite constant. Thus, women today will spend a much greater portion of their life in the postmenopausal state as compared to their counterparts of the previous century. While a number of mechanisms may contribute to reproductive decline, this review will focus upon data supporting an age-related *hypothalamic* defect as an important contributing factor to reproductive aging. The majority of studies in this area have been performed in rodent animal models, and thus, this review will be heavily focused upon findings from such models. However, where available, studies in humans will also be presented and discussed in context with the findings in rodent animal models.

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2. Evidence of a hypothalamic defect in reproductive aging

Female rats and mice become acyclic at 17–21 months, following a period of irregular reproductive cycles [1–3]. One postulated hypothesis for age-related acyclicity is that the ovarian pool of oocytes simply undergoes depletion with advancing age [7–9]. While depletion of oocytes occurs with aging and is generally accepted as the ultimate cause of cessation of cycles, there is a growing body of evidence suggesting that a hypothalamic defect is a critical contributing factor for the transition from regular to irregular cycles. This suggestion is supported by the observation that transplantation of ovaries from old rats to the kidney capsule of regularly cycling, but previously ovariectomized young rats resulted in follicular development and ovulation [10,11]. Furthermore, grafts of fetal hypothalami placed in the third ventricle of old rats restored ovarian weight and the appearance of follicles at various stages of development [10,12]. Additional work has shown that electrical stimulation of the hypothalamus or administration of centrally acting drugs is also capable of returning reproductive function in aged animals [13,14]. These studies suggest that defects in the neuroendocrine axis contribute significantly to the transition from regular to irregular cycles, while exhaustion of ovarian follicles contributes predominantly to cessation of cycles. Fig. 1 illustrates the multiple levels and intricate hormonal feedback regulation of the hypothalamus–pituitary–ovarian (HPO) axis in females. The numbers in the diagram correspond to control points, which may be altered in aging and could contribute to a hypothalamic defect and reproductive aging. Item #1 in the diagram corresponds to a proposed hypothalamic defect involving an altered release of gonadotropin hormone-releasing hormone (GnRH), the key central regulator of reproduction. This defect in GnRH secretion may be due to altered neurotransmitter control (as indicated by #2 in Fig. 1). Due to the interconnectivity of the various components of the HPO feedback axis, alterations in other levels of the HPO axis (e.g. anterior pituitary and ovary) could also contribute to hypothalamic dysfunction and reproductive aging (see items #3–5, Fig. 1). In the subsequent sections below, the evidence for a defect in hypothalamic GnRH secretion will be examined, as well as the potential underlying mechanisms for the defect.

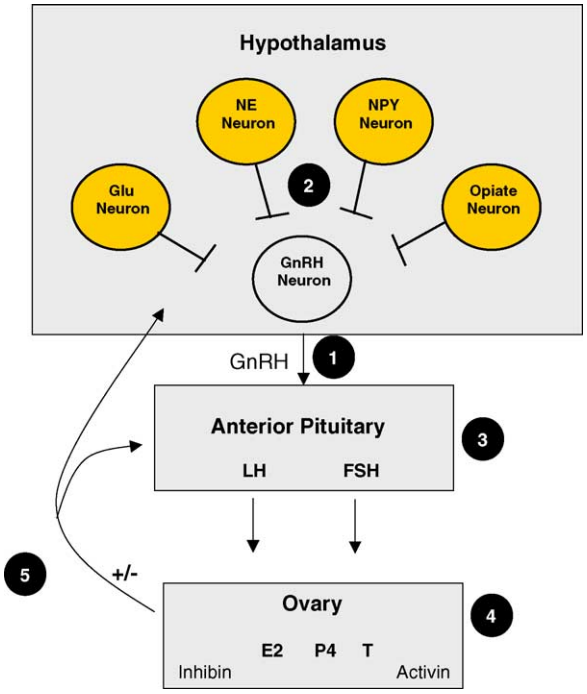

Fig. 1. Diagram illustrating the intricate feedback regulatory loop of the hypothalamic–pituitary–ovarian (HPO) axis and potential sites of defects in reproductive aging (indicated by circled numbers). The diagram illustrates only some of the factors involved in the intricate feedback regulatory loop of the HPO axis. See text for further description.

3. Age-related alterations in GnRH and gonadotropin secretion

3.1. GnRH and luteinizing hormone (LH)

A number of studies have documented that prior to becoming acyclic, normal cycling middle-aged rats display a significantly *attenuated* proestrous LH surge (Fig. 2) [15–18] for review. As shown in Fig. 2, work from Rubin's laboratory measured GnRH neurosecretion in vivo from the medialbasal hypothalamus (MBH) of young and middle-aged ovariectomized female rats during the steroid-induced LH

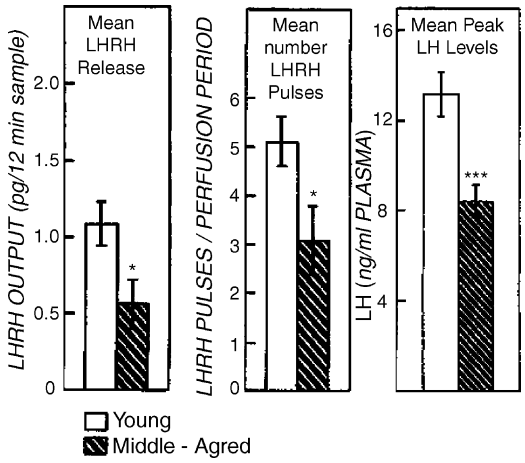

Fig. 2. Measurements of in vivo GnRH (LHRH) output in the medial basal hypothalamus and serum LH levels on the day of a steroid-induced LH surge in ovariectomized young and middle-aged females. At the time of ovariectomy, the young females were 3–4 months old and the middle-aged females were 10–12 months old. As depicted, the overall mean levels of GnRH output were significantly lower in middle-aged relative to young females, and the mean number of GnRH pulses detected during the period of perfusion was also diminished in middle-aged females. It is likely that the decline in GnRH release contributed to the attenuated peak levels of serum LH that were measured in conjunction with the LH surge in middle-aged relative to young females. From Rubin [18], with permission; $*P < 0.05$; $***P < 0.001$.