

**INFLUENCE OF ESTROGEN ON AGING OF THE CENTRAL NERVOUS SYSTEM:
ITS ROLE IN DECLINING FEMALE REPRODUCTIVE FUNCTION***

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INTRODUCTION

In many mammalian species menopause, or the cessation of regular reproductive cycles, occurs when individuals are middle aged (Ingram, 1959; Mandl, 1961; Treloar et al., 1967; Huang and Meites, 1975; Treloar, 1981). It has long been thought that exhaustion of ovarian follicles determines the timing of the onset of reproductive senescence (Costoff and Mahesh, 1975; Richardson et al., 1987). More recently it has become clear that hypothalamic function may change during middle-age and that this change may contribute to the cascade of events that leads to acyclicity (Wise, 1983; Finch et al., 1984; Nelson and Felicio, 1987). Although the majority of evidence supporting to the concept that the central nervous system plays an important role in the aging of the female reproductive system comes from studies with laboratory animals, observations in the human female also support this concept. First, the data of Richardson and colleagues (1987), in combination with those of Block (1952), suggest that the rate of follicle depletion accelerates dramatically during the last decade of menstrual life. Furthermore, the number of follicles below which cyclicity ceases to be regular is highly variable. These observations, in turn, suggest that the neuroendocrine environment that regulates the rate of follicular growth and development may change during middle age and may contribute to the perimenopausal transition. Second, hot flashes occur in a significant proportion of aging women (Casper and Yen, 1983; Judd,

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1987). Since the hypothalamus regulates body temperature, these findings suggest that age-related changes occur in the central nervous system and are involved in the establishment of the menopausal state. Hot flashes occur in close temporal association with the pulsatile release of LH (Casper and Yen, 1979; Tataryn et al., 1979). However, the pulsatile secretion of GnRH does not directly stimulate the occurrence of hot flashes since temperature instability persists in the absence of the pulsatile release of LH that is associated with pituitary insufficiency (Meldrum et al., 1981), surgical hypophysectomy (Mulley et al., 1977) or treatment with agonists of GnRH (Casper and Yen, 1981; DeFazio et al., 1983). Together, these data suggest that age-related alterations in hypothalamic function occur in women and can account simultaneously for changes in both thermoregulation and the release of LH. Third, the ability of estradiol to induce a positive feedback response in perimenopausal women appears to be compromised. Van Look et al. (1977) found that estradiol induces an LH surge in a lower percent of older than younger women. In postmenopausal women, the estradiol-induced release of LH is pulsatile and erratic in nature, unlike the more sustained and regular increase that can be stimulated in young women. Finally, the variability of hormonal patterns that accompanies the perimenopausal period is great and suggests that multiple factors play important roles in the transition to the menopause. In some women, hormonal patterns are indistinguishable from those seen in fertile young women; in other women, levels of gonadotropin and estrogen are typical of postmenopausal women (England et al., 1974; Furuhashi et al., 1977; Reyes et al., 1977; Van Look et al., 1977). Indeed, the variation in hormonal levels, the relationships between and progression of endocrine changes through the perimenopausal period within a single aging individual are not easily explained and do not exhibit an unbroken movement from normality through moderate disturbances to the postmenopausal state. Thus, data from both longitudinal and cross-sectional studies suggest that the transition to menopause is a multifactorial process involving neural and ovarian factors.

The positive and negative feedback effects of estrogen upon the function of the central nervous system are essential for cyclic reproductive function. Many investigators believe that (1) age-related alterations in the ability of acute changes in levels of estrogen to influence the secretion of gonadotropin, and (2) the cumulative effects of exposure to endogenous estrogen on reproductive aging contribute to the

cascade of complex events that result in acyclicity and infertility (for reviews see Lu, 1983; Wise, 1983; Finch et al., 1984; Nelson and Felicio, 1985; Nelson and Felicio, 1987). These two topics will be reviewed in this chapter.

INFLUENCE OF ESTROGEN ON AGING OF THE CENTRAL NERVOUS SYSTEM

Effects of Acute Estrogen Treatment in Aging Animals

Although estrogen therapy is commonly used in postmenopausal women, few studies have been designed to compare the negative or positive feedback effects of estrogen treatment in young and older women (reviewed in Judd, 1987). The results of the few studies are controversial. In perimenopausal women between 37 and 52 years of age, Van Look et al. (1977) found that a smaller proportion of women responded positively to estrogen. In this study, 3 days of treatment with ethynodiol diacetate was less effective in suppressing LH and in inducing LH surges in older than in younger women. In contrast, Tanaka and Katayama (Tanaka and Katayama, 1982) found that intravenous injection of conjugated estrogen elicited normal release of LH in women as old as 49 years of age. In postmenopausal women, estrogen treatment appears to cause both a negative and a positive feedback response. However, the augmented release of LH is oscillatory and erratic in nature (Yen and Tsai, 1971).

In laboratory rodents, age diminishes the ability of steroids to induce a surge of gonadotropin. We (Wise, 1984) observed an alteration in estradiol-induced surges of LH in middle-aged, previously irregularly cycling rats. Young (3- to 4-month-old) and middle-aged (9- to 11-month-old) rats were ovariectomized for 1 week and then treated with physiological concentrations of estradiol for 1, 2, 3 or 4 days (Figure 1). The data show that a longer period of exposure to estradiol is required before an LH surge occurs in the majority of middle-aged rats. That is, while most young rats display LH surges after two days of exposure to estrogen, most middle-aged rats respond only after 3 days of exposure to estrogen. Despite the presence of equivalent concentrations of plasma estradiol, the amplitude of the LH surges in middle-aged rats is attenuated compared to those in young rats. In addition, LH surges are delayed with respect to the time of onset. Lu et al. (1977) also found that previously

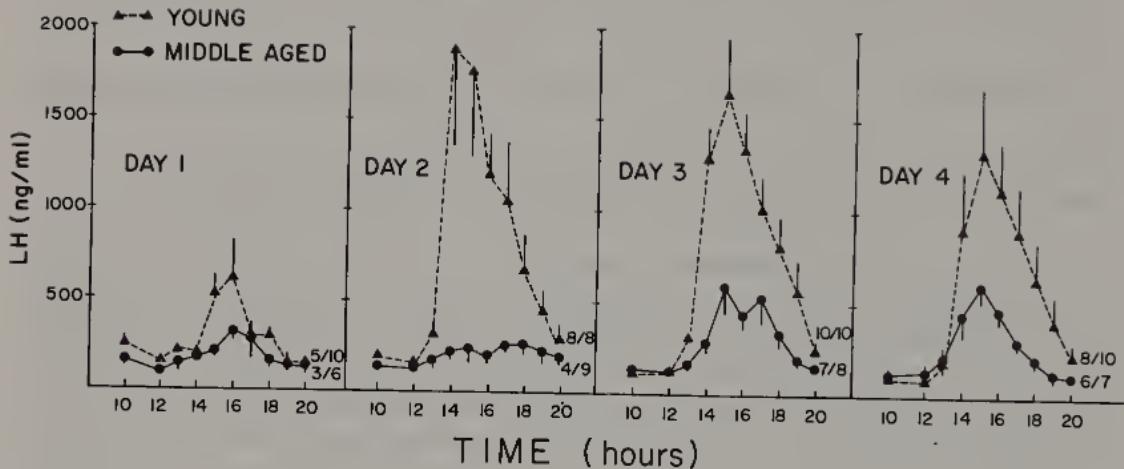


Figure 1. Plasma concentrations of LH in ovariectomized young and middle-aged rats, treated with Silastic capsules containing estradiol for 1, 2, 3, or 4 days. The fraction at the end of each LH profile indicates the ratio of the number of rats that displayed an LH surge to the total number of rats bled. The steroid-induced surge in LH was attenuated and delayed in middle-aged, as compared to young rats. (Wise, 1984)

irregularly cycling rats, when ovariectomized and treated sequentially with estradiol and progesterone 1-2 months later, exhibit attenuated surges of LH. Previous reproductive status influences the ability of steroids to induce surges of LH, since a positive feedback effect is further attenuated or totally absent in middle-aged, previously constant estrous (Gray and Wexler, 1980; Rubin et al., 1985) or older animals (Lu et al., 1977; Peluso et al., 1977; Lu et al., 1980; Steger et al., 1980).

Several neurotransmitters regulate the estradiol-induced release of LH (for review see Barraclough and Wise, 1982; Ramirez et al., 1984; Kalra, 1986). In particular, there is considerable evidence to suggest that monoamines

play an important regulatory role in the cyclic and steroid-induced release of LH and that estradiol may feedback to regulate the LH surge through a monoaminergic mechanism. Therefore, age-related changes in the ability of estradiol to induce an LH surge may be due to changes in the ability of estradiol to influence neurotransmitter activity in aging animals. We (Wise, 1984) tested this hypothesis using the animal model described above. Young and middle-aged rats were ovariectomized and 1 week later they were treated with estradiol. Norepinephrine activity was examined, 2 and 4 days after estradiol implantation, in several specific hypothalamic nuclei at 1000 hrs, when concentrations of LH were basal and at 1500 hrs, when the LH surge occurs (Figure 2). We found that, in young animals, norepinephrine turnover is low in the morning and elevated during the afternoon in the anterior hypothalamic nuclei (suprachiasmatic and the medial preoptic nuclei) and in the medial basal hypothalamic area (median eminence). In middle-aged rats, no increase was observed during the afternoon in the two anterior hypothalamic areas. The absence of a diurnal pattern of turnover rates in middle-aged rats is not simply because due to the fact that rates and/or concentrations are uniformly lower in these rats. Instead it appears that, in middle-aged rats, estradiol frequently cannot depress turnover rates during the morning. Thus, there is a relatively steady rate of turnover during the entire day with no significant increase during the time of the expected LH surge. The data demonstrate that age-related alterations in norepinephrine turnover are initially limited specifically to the suprachiasmatic-preoptic area of the hypothalamus. The suprachiasmatic nucleus is known as a "biological clock" because it is a critical endogenous neural pacemaker area of the brain which entrains and regulates the timing of many circadian rhythms (for reviews see Inouye and Kawamura, 1979; Schwartz et al., 1980; Inouye and Kawamura, 1982; Moore, 1983). Destruction of this area of the brain disrupts the rhythmicity of virtually all physiological functions, including cyclic reproductive function (Brown-Grant and Raisman, 1977; Raisman and Brown-Grant, 1977; Stephan and Nunez, 1977). Thus, our data point to the possibility that aging involves initial changes in the function of this critical area which can have multiple important repercussions as animals continue to age.

It is important to consider whether other neurotransmitters, involved in reproductive cyclicity and diurnal rhythms, are also affected during aging and whether estrogen

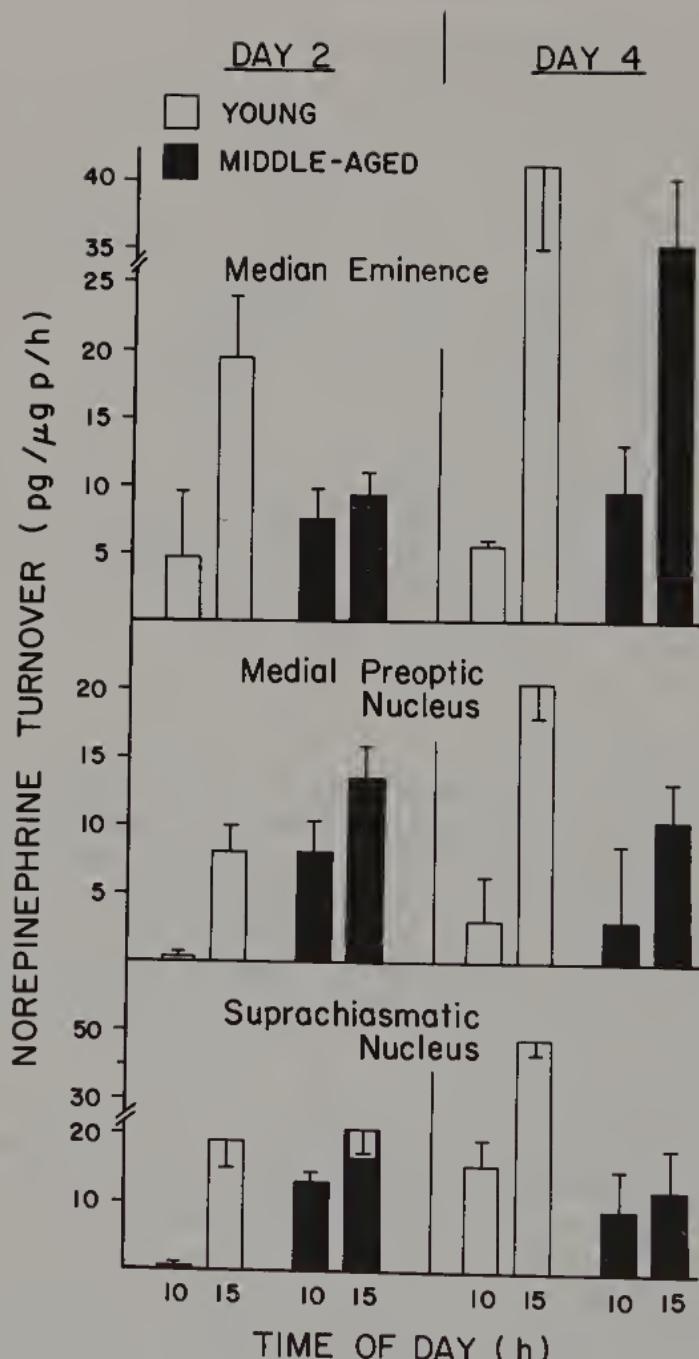


Figure 2. Rates of turnover of norepinephrine in the median eminence, medial preoptic nucleus and suprachiasmatic nucleus of young and middle-aged rats. Turnover was significantly higher during the afternoon than in the morning in all hypothalamic areas of young rats on day 2 and day 4. In contrast, in middle-aged rats, turnover was higher during the afternoon only in the median eminence on day 4. No diurnal rhythm was observed in other hypothalamic nuclei. (Wise, 1984).

influences these changes. Serotonin is a second neurotransmitter that modulates cyclic release of LH (Kordon et al., 1981; Walker, 1980; Walker, 1983; Walker and Wilson, 1983), and this neurotransmitter system has been implicated as one of the systems that relays circadian information (Kordon et al., 1981). We investigated whether serotonin turnover exhibits a diurnal rhythm in ovariectomized and estradiol-treated rats, and whether aging influences this rhythm (Cohen and Wise, 1988). The same estradiol-treated, young and middle-aged animal model was used as described above. Serotonin turnover was determined at 0800 hrs, 1200 hrs, 1800 hrs and 2400 hrs in several specific hypothalamic nuclei, including the suprachiasmatic nucleus. In young ovariectomized rats, serotonin turnover rates in the suprachiasmatic nucleus exhibit a distinct diurnal rhythm: turnover rates are higher during the light period than during the dark (Figure 3). Estradiol treatment reverses this rhythm. No diurnal rhythm was detectable in either ovariectomized or estradiol-treated middle-aged rats. Thus, aging influenced the diurnal rhythm of this important neurotransmitter in this critical neural pacemaker area of the brain.

It appears that changes in the pattern of monoamine turnover influence the pattern of release of GnRH. Rubin and Bridges (1986) analyzed the effects of treatment with estradiol and progesterone on the release of GnRH using the push-pull perfusion method in young and middle-aged rats. They attempted to estimate the rate of release of GnRH in the area of the median eminence prior to and during the time of the expected LH surge. Although peak concentrations of GnRH do not differ between the age groups, the overall profiles of GnRH are different: more samples collected from middle-aged rats were below the level of detectability, and basal concentrations of GnRH one hour prior to the expected time of the steroid-induced surge in LH were significantly lower in the older rats.

In summary, the ability of estradiol to feedback and influence hypothalamic function deteriorates with age in both humans and laboratory animals. Data suggest that this deterioration results in alterations in the pattern of release of gonadotropin by the time subjects are middle-aged and entering the transition to the acyclic or postmenopausal state.

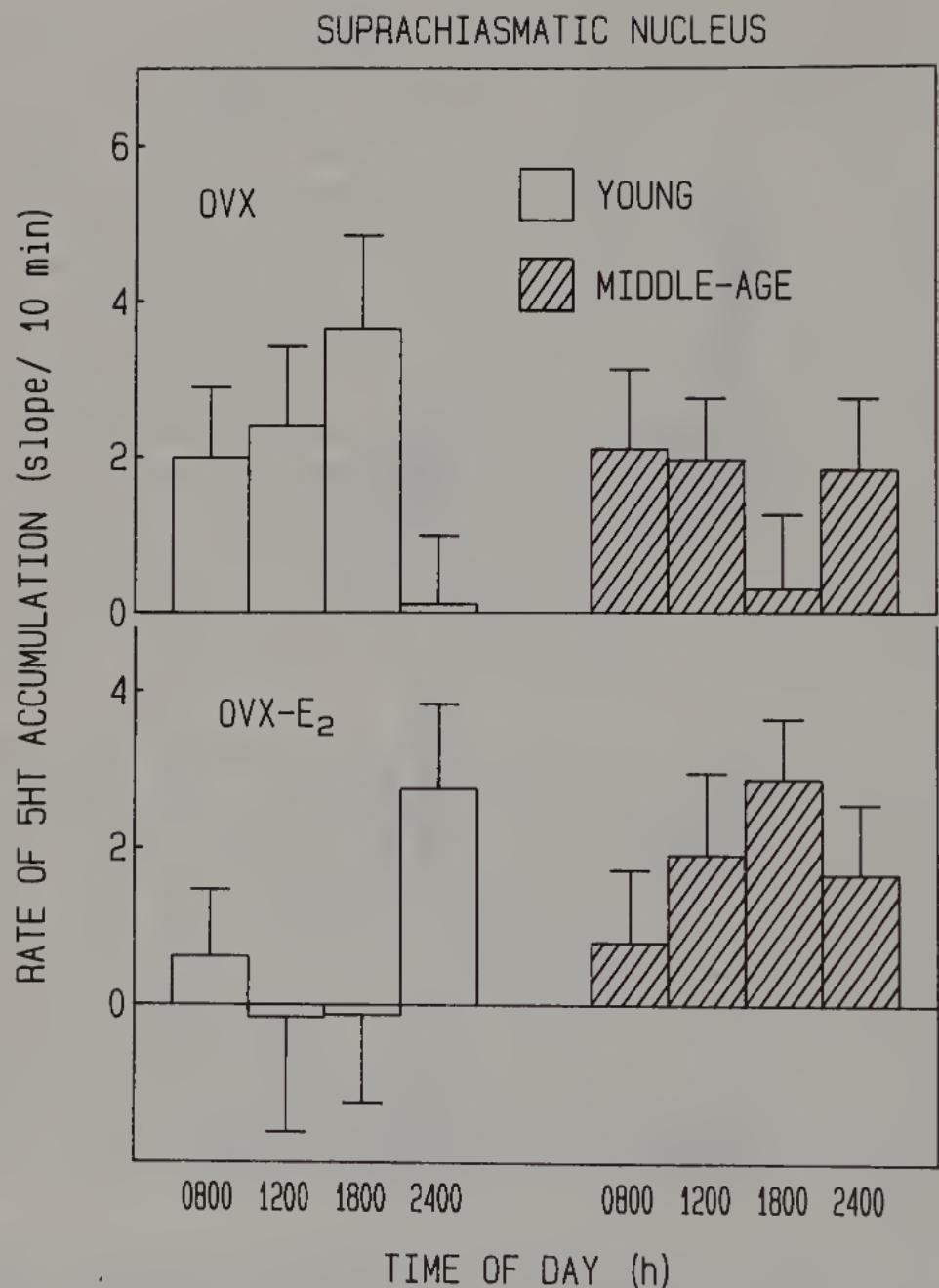


Figure 3. Rate of accumulation of serotonin (5HT), after treatment with pargyline, in the suprachiasmatic nucleus of ovariectomized and ovariectomized, estradiol-treated, young and middle-aged rats. In young ovariectomized rats serotonin turnover was higher during the light than during the dark period. Estradiol reversed this rhythm. No detectable rhythm was observed in middle-aged ovariectomized or estradiol-treated rats.

Cumulative Effects of Exposure to Endogenous Estrogen

During the past twenty years, the possibility that the hormonal environment may regulate the rate of aging has been investigated with increasing interest. It appears that many of the changes associated with age are not necessarily irreversible or absolutely determined by the chronological age of the organism. Many changes can be accelerated, reversed, suppressed or delayed by manipulations of the endocrine environment. It is particularly noteworthy that the concept that exposure to variable and cycling levels of hormone may influence the rate of aging may also apply to other endocrine axes. Data regarding the deleterious effects of adrenal corticosteroids on the central nervous system and the converse effects of deprivation of adrenal hormones are well-documented (reviewed in Landfield, 1978a,b; Landfield et al., 1980; Sapolsky et al., 1986). Thus, treatment with estrogen (Brawer et al., 1978; Brawer et al., 1980b; Schipper et al., 1981; Mobbs et al., 1984a), even within the physiological range (Kohama et al., 1988), advances the onset of age-associated changes in reproductive function (for review see Finch et al., 1984; Nelson and Felicio, 1985; Nelson and Felicio, 1987). When pharmacological concentrations of estrogen are administered as a bolus injection to young adult rats (Brawer et al., 1978; Brawer et al., 1980b; Garcia-Segura et al., 1986; Leranth et al., 1986) or mice (Mobbs et al., 1984a) the animals become permanently acyclic and exhibit persistent vaginal cornification characteristic of reproductive senescence. Injection of estradiol valerate into adult female rats impairs the regulation of LH (Leranth et al., 1986) and is correlated with degenerative lesions in some axons, axon terminals, and dendrites of the arcuate nucleus, and an increase in the number of reactive glial cells (Garcia Segura et al., 1986) in this area of the hypothalamus. Similarly, estradiol-injected mice exhibit impairments in regulation of LH levels similar to those seen in old, acyclic mice: one month after ovariectomy, plasma levels of LH were 40% lower and estradiol-induced surges of LH were 60% lower than in controls. Furthermore, mice treated with estradiol valerate are unable to support estrous cycles when given young ovarian grafts, in contrast to controls (Mobbs et al., 1984a). Moreover, sustained physiological levels of plasma estradiol achieved by estradiol implants (Mobbs et al., 1984a) or by inclusion of estradiol in the drinking water (Kohama et al., 1988) also produce long-lasting reproductive impairment. Mobbs et al. (1984a) found that if mice carried estradiol implants for six weeks, only 50% of the

mice exhibited estrous cycles upon removal of the implant, compared with 100% of the sham-implanted controls. These treatments do not appear to impair ovarian or pituitary function or the GnRH neurons, yet the results appear to require the presence of the ovary since ovariectomy prior to treatment with estrogen prevents the glial reaction (Brawer et al., 1980a).

Conversely, partial or total deprivation of estrogen, achieved through repeated breeding (Nass et al., 1982; Lu et al., 1985), administration of progesterone (Lapolt et al., 1986) or long-term ovariectomy (Felicio et al., 1983; Mobbs et al., 1984a,b; Wise et al., 1988), prolongs reproductive lifespan or potential. Lu and colleagues (1985) prevented the cyclic increase in estradiol by two means: (1) caging females with males and allowing them to bear young, or (2) treating females with progesterone for three weeks out of every four for a period of five months. They found that the period of regular estrous cyclicity and fertility is maintained for an extended period of time in these animals as compared to untreated controls. Furthermore, preovulatory surges of LH in 15-month-old rats which were repeatedly mated and in 19-month-old rats which had received progesterone implants are comparable to those observed in young rats and significantly greater than in middle-aged, non-treated rats (Nass et al., 1982; Lu et al., 1985). Total deprivation of estrogen for a prolonged period during adult life, achieved through ovariectomy when animals are young, delays age-associated changes in reproductive capacity (Felicio et al., 1983), the ability of estradiol and progesterone to induce LH surges (Lu et al., 1977; Blake et al., 1983; Scarbrough and Wise, unpublished observations) and the pulsatile pattern of gonadotropin secretion (Blake et al., 1983; Wise et al., 1988). Felicio et al. (1983) ovariectomized mice at 5, 17 and 25 months of age and transplanted ovaries from 5-month-old donors. They found that the ovaries of young mice can restore estrous cyclicity in old hosts, suggesting that the ovary plays a major limiting role in the ability of mice to cycle as they age. Of particular importance was the finding that cyclicity can be almost completely restored and can be extended for a longer period of time if the aging hosts have been deprived of estrogen for the majority of their lives. Thus, long-term ovariectomy delays, but does not completely stop the age-related decline in cycling potential.

The absence of ovarian steroids for prolonged periods of time also restores the ability of estradiol to have a

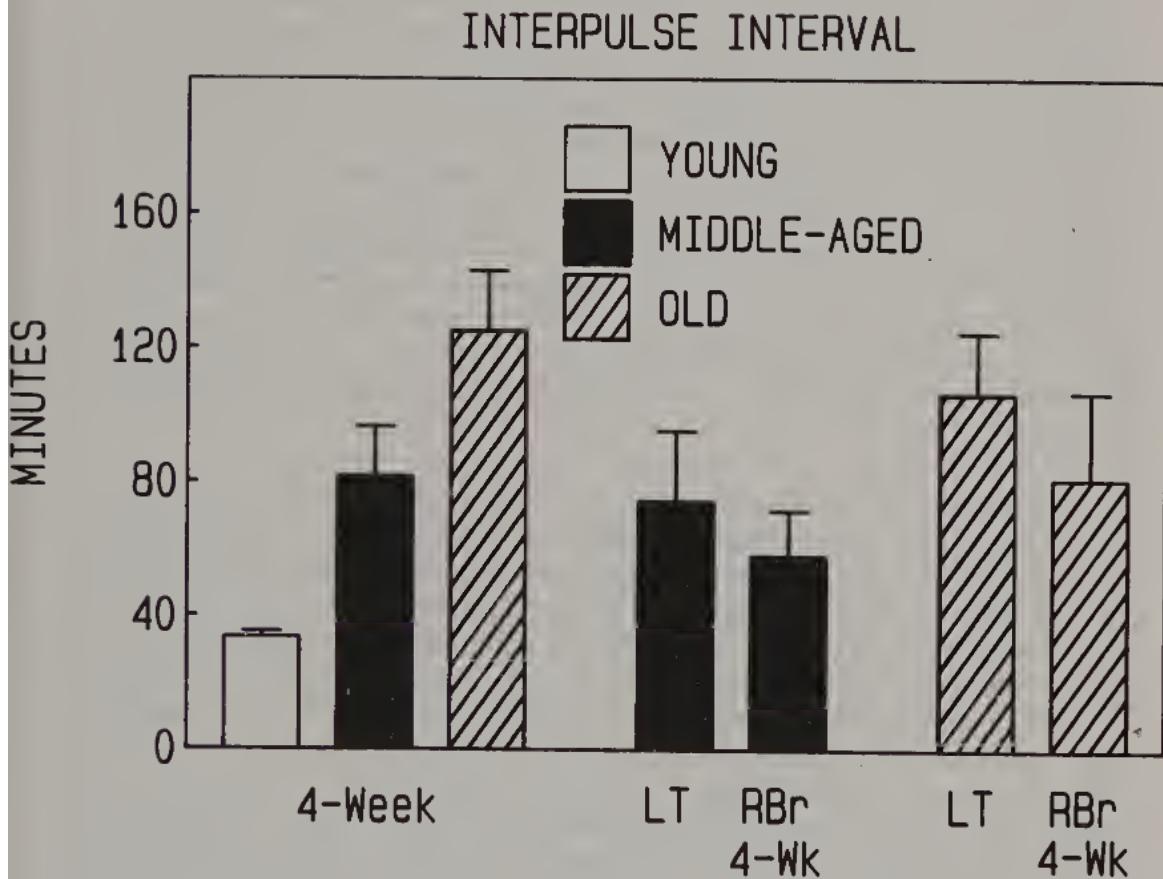


Figure 4. Interpulse intervals of LH pulses. Interpulse intervals in young, middle-aged and old ovariectomized rats were significantly different from each other. Age-related changes in interpulse interval were not affected in middle-aged or old rats by long-term ovariectomy or repeated pregnancies. (Wise et al., 1988)

positive feedback effect on the release of gonadotropin. Lu et al. (1981) found that previously constant-estrous rats which are ovariectomized and treated acutely with estradiol and progesterone do not exhibit an LH surge. However, when

they are ovariectomized five weeks prior to treatment with steroids, a robust surge of LH can be elicited. Similarly, we have found that middle-aged rats, which are ovariectomized when young, are able to respond to physiological concentrations of estradiol: LH surges are equivalent in amplitude and timing to those in young controls and are significantly greater than those in middle-aged rats that have been ovariectomized for one week (Scarborough and Wise, unpublished observations). Furthermore, preliminary data suggest that long-term ovariectomized, estradiol-primed rats are able to generate an LH surge as a result of a diurnal pattern of norepinephrine activity in the median eminence that resembles the diurnal pattern in young animals and does not show the age-related decline characterized by their middle-aged, untreated counterparts (Scarborough and Wise, unpublished observations).

Together these data suggest that exposure to endogenous estrogen has a cumulative, deleterious effect on the reproductive axis. The experimental observations discussed above establish that long-term diminished exposure to estrogen prolongs the ability of animals to respond positively to estrogen and, thereby, prolongs the period of estrous cyclicity and fertility. However, these studies do not address the question of whether the estrogen milieu can modulate the rate of aging of hypothalamic functions that are maintained in the absence of estrogen, such as pulsatility of hypothalamic GnRH neurons. The frequency of GnRH pulses, measured by quantitating the frequency of LH pulses in peripheral blood, is thought to reflect the integrity of the "neural pulse generator."

It is important for us to understand whether aging affects the neural pulse generator and whether acute or chronic exposure to estrogen influences aging of this pacemaker, because this fundamental ultradian rhythm of the central nervous system is thought to integrate a wide variety of somatic, visceral and behavioral functions throughout the day and night (Rasmussen, 1986). Therefore, if the integrity of the pulse generator deteriorates with age, we may expect repercussions in a variety of apparently independent functions that are unrelated to the reproductive system per se.

We attempted to assess the integrity of the neural pulse generator in aging rats by measuring the frequency of LH pulses (Wise et al., 1988). To determine whether estrogen modulates the rate of aging, we also examined this parameter

in long-term ovariectomized rats and in animals that had been used as breeders. Young (2- to 3-month-old), middle-aged (7- to 8-month-old) and old (15- to 18-month-old) rats were ovariectomized and used one month later. Other rats were ovariectomized when young and were used when they were middle-aged or old. Finally, to test the effect of partial deprivation of estrogen, rats were used by the supplier as breeders, ovariectomized when they were middle-aged or old, and used in the experiment after one month. The results of this study established that age-related, hypothalamo-pituitary dysfunction is reflected in alterations in all parameters of LH secretion that we examined: the percent of rats exhibiting a pulsatile pattern of LH secretion decreases, mean concentrations of LH and amplitude of LH pulses decrease, and the frequency of LH pulses increases by the time rats are middle-aged (Figure 4). Diminished exposure to estrogen during the reproductive lifespan has a sparing effect on the mean concentration of LH and amplitude of LH pulses. In marked contrast, age-related changes in the frequency of LH pulses are not prevented by long-term ovariectomy or breeding. Since the frequency of pulsatile secretion of hormone reflects the integrity of the neural pulse generator, these data suggest that aging of this important pacemaker is not modulated by the hormonal milieu.

In summary, the data from studies in both human females and laboratory animals suggest that the menopause is caused by multiple endocrine factors which include changes in the pattern of neuroendocrine events and in the ability of estrogen to influence the central nervous system. Data from studies in laboratory animals suggest that exposure to estrogen during the reproductive lifespan may modulate the rate of aging. It will be important to determine whether this concept is applicable to humans.

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