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GONADOTROPIN SECRETION DURING AGING IN WOMEN: REVIEW ARTICLE

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Abstract—Biological aging during the postmenopause markedly affects the neuroendocrine control of gonadotropin release. The determination of the age-related dynamics on gonadotropin secretion in postmenopausal women has proven to be a valid approach for delineating changes as a function of progressive age. As a result, major functional derangements, primarily at a hypothalamic rather than a pituitary site, have been determined as concomitants of aging in women. Furthermore, aging may impair the negative feedback sensitivity to ovarian sex steroids, and interfere with the central neurotransmitter activity governing gonadotropin secretion. The data reviewed on gonadotropin secretion in postmenopausal women support the view that the age-related processes are related to a hypothalamic rather than to a pituitary hypofunction.

Key Words: Postmenopause, hypothalamus, pituitary, gonadotropins, aging, neurotransmitter, sex steroids, feedback

INTRODUCTION

OVER THE PAST two decades our understanding of the neuroendocrine processes of aging has been considerably enlarged. Results from recent investigations regarding the neuronal processes involved in aging have attracted increasing interest. It is now generally acknowledged that endocrine function shows age-related changes from the very beginning of development. Thus, neuroendocrine alterations observed during transition states such as the menopause may only coincidentally be related to this period. In fact, endocrine alterations at this time may represent the sum of functional aberrations that were initiated much earlier in life (Meites *et al.*, 1982). Evidence has accumulated to suggest that neuroendocrine aging may rather relate to changes in the interrelationship

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between hormonal and neural signals rather than to discrete neuroendocrine events (Timiras, 1983).

The cessation of menstrual cyclicity during the menopause represents a biological hallmark in the chronobiology of female life, and indicates the end of female reproductive capacity. During this transition period, the progressive decline in sex steroid secretion from the ovaries precipitates profound alterations in the neuroendocrine regulation of the reproductive system. This state of hypergonadotropic hypogonadism during the postmenopausal years represents a prolonged period of endocrine stability during which the sex steroid milieu remains virtually unaltered. Hence, this time provides a unique baseline to delineate age-related alterations in the neuroendocrine control of reproductive hormone release. Determination of the changing gonadotropin dynamics during aging in postmenopausal women may thus prove to be useful in facilitating a more profound understanding of the principal mechanisms involved in the aging of endocrine systems. In particular, alterations in the hypothalamic and anterior pituitary function can be discerned as neuroendocrine concomitants of progressive age, because uncertainty exists as to whether aging of the reproductive system involves a hypothalamic decline rather than pituitary hypofunction (Timiras, 1983). Furthermore, the sensitivity of the central regulatory units to sex steroid feedback may severely be impaired by progressive age (Steger and Peluso, 1987). Central neurotransmitter activity implicated in the control of gonadotropin release may also be altered (Meites *et al.*, 1982).

To address some of the mechanisms presumed to be involved in the process of neuroendocrine aging, we have aimed at determining serum gonadotropin pulsatility in postmenopausal women. This approach of evaluating age-related processes in humans appears to be justified, because it is founded on the demonstration of tight functional and temporal links between hypothalamic signals and pituitary gonadotropin release (Clarke and Cummins, 1982). Therefore, changes in the serum gonadotropin profiles may reflect the sum of altered neuroendocrine function occurring with progressive age in postmenopausal women. In addition, determination of gonadotropin-releasing hormone (GnRH)-stimulated gonadotropin secretion may discriminate between age-related hypothalamic and pituitary affections. Secretory dynamics determined in this way probably reflect collective age-related alterations in the neuroendocrine mechanisms governing gonadotropin release in postmenopausal women.

CHARACTERIZATION OF ULTRADIAN AND CIRCADIAN VARIATIONS IN LH PULSATILITY IN POSTMENOPAUSAL WOMEN

The secretion of gonadotropins is invariably increased in postmenopausal women (Hammond and Ory, 1985; Rossmanith *et al.*, 1990; Rossmanith *et al.*, 1991a,b). Because significant negative feedback by ovarian sex steroids on the hypothalamopituitary system is lacking after the onset of the menopause (Yen, 1991), gonadotropin release may enhance as consequence of an open feedback loop. In the early perimenopausal years, the concentrations of follicle-stimulating hormone (FSH) rise initially, which is then followed by a gradual increase in luteinizing hormone (LH) levels (Judd *et al.*, 1978; Hammond and Ory, 1985). The secretion of gonadotropins has been recognized to be episodic ("pulsatile") in nature (Knobil, 1980; Rossmanith *et al.*, 1990). In fact, these LH pulse characteristics become prominent in women in the postmeno-

pausal period compared to normally cycling women. Because gonadotropin secretion patterns in postmenopausal women are unaffected by ovarian sex steroid influences (Rossmanith *et al.*, 1991a,b), the pulse attributes of this basic rhythm may reflect the maximal activity of the central pulse generator (Rossmanith *et al.*, 1990; Rossmanith *et al.*, 1994).

In the LH secretory profiles of postmenopausal women, the pulses are set at a frequency similar to those of normally cycling women, albeit with much higher pulse amplitudes (Fig. 1). That this LH pulsatility indeed represents the maximal release rate of the central GnRH-LH pacemaker is demonstrated by the finding that increases and decreases in LH pulse attributes in women during the menstrual cycle are limited by the pulse characteristics of postmenopausal subjects. In particular, the LH pulse frequency represents a threshold which is never exceeded by the changing LH pulse attributes during the menstrual cycle (Rossmanith *et al.*, 1990). Because the LH pulse frequency determined in gonadotropin profiles of postmenopausal women compare to those found for the spontaneous pulsatile GnRH release from human hypothalami in vitro (Rasmussen *et al.*, 1989), it is suggested that the LH release frequencies indeed reflects an

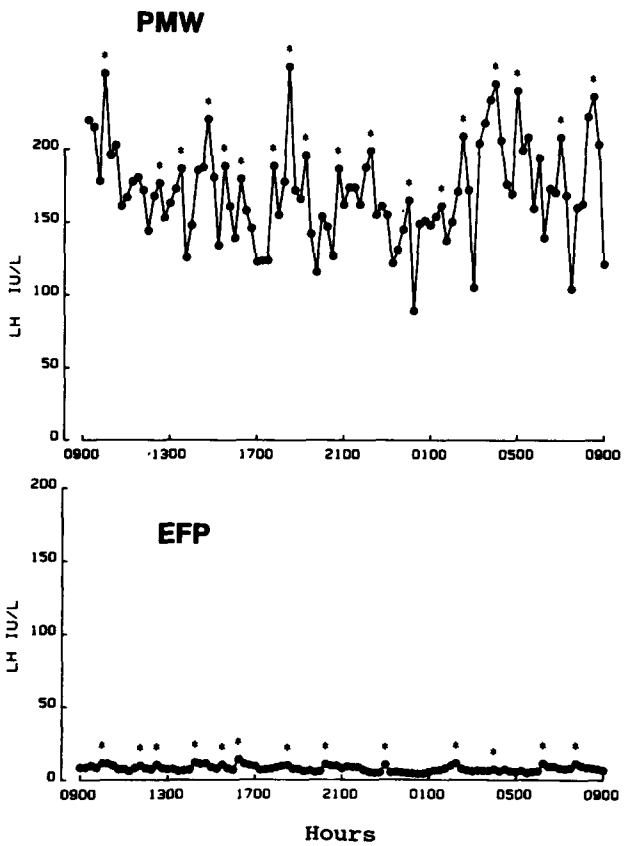

FIG. 1. Twenty-four-hour LH secretory profiles in a woman during the postmenopause (PMW, top) and in a woman during the early follicular phase of her cycle (EFP, bottom). *Significant pulses.

unrestrained pulse rhythm. Even during periods with increasing serum concentrations of sex steroids, as during the menstrual cycle (including the midcycle LH surge), the LH pulse attributes approximate those of postmenopausal women. In the presence of residual serum androgen concentrations, this basic pulse rhythm remains unrestrained, because androgen receptor blockade fails to noticeably accelerate the LH pulsatility of postmenopausal women (Rossmanith *et al.*, 1991a). Similarly, changing LH pulsatility during ovarian sex steroid replacement in postmenopausal women (Fig. 2) is also confined to the pulse attributes of the unrestrained LH rhythm during unreplaced conditions (Rossmanith *et al.*, 1994a). Collectively, the changing LH pulsatile attributes during high sex steroid exposure, as during the menstrual cycle or during hormone replacement, are limited by the characteristics of the unrestrained pulsatility observed during the unreplaced state in postmenopausal women (Rossmanith *et al.*, 1994a).

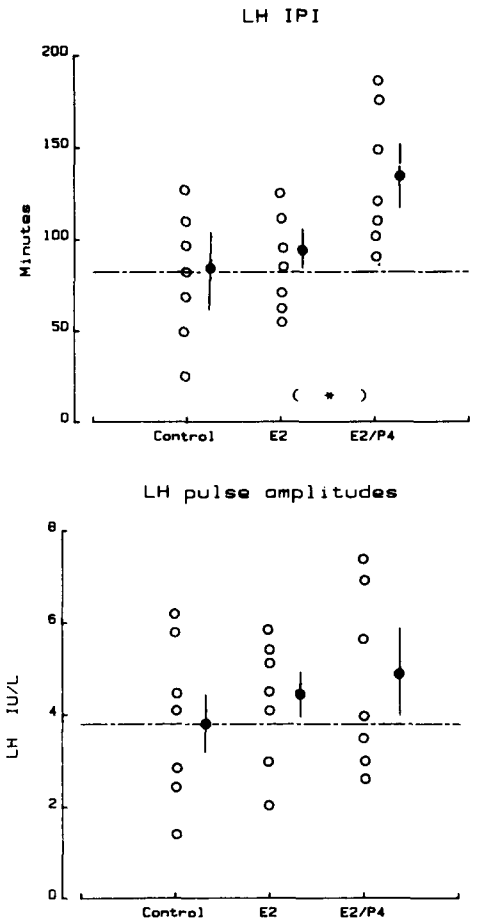

FIG. 2. Mean (± SEM) LH interpulse intervals and pulse amplitudes of seven postmenopausal women before replacement (= control) and during E_2 or E_2/P_4 replacement regimens. The horizontal line indicates the mean values during control conditions. $^*p < 0.05$ versus values linked with brackets.

Moreover, gonadotropin release in postmenopausal women is characterized by a circadian variability on which ultradian secretory episodes of gonadotropin secretion are superimposed (Rossmanith and Lauritzen, 1991; Mortola *et al.*, 1992). Recent investigations have disclosed a circadian rhythm not only for the mean gonadotropin secretion rates, but also for the magnitudes of the pulse attributes (Rossmanith and Lauritzen, 1991). The characteristics of these circadian swings vary in accordance with the prevailing sex steroid milieu, and are thus different in postmenopausal from normally cycling women. In postmenopausal women, highest LH pulse amplitudes are found during the night hours, at about the time when maximal LH secretion is attained (Rossmanith and Lauritzen, 1991). The preservation of a circadian rhythm in pulsatile LH secretion during the years of the early postmenopause is in keeping with the notion that the endocrine system remains responsive despite advancing of age (Timiras, 1983). This diurnal variability in gonadotropin secretion remains during senescence (Haus *et al.*, 1989), although a subtle time-shift or an attenuation of this rhythmicity cannot be excluded in elderly women. Alterations in the circadian variability of hormone release have been assumed to be responsible for the age-related deficit in endocrine performance (Timiras, 1983).

EPISODIC GONADOTROPIN SECRETION DURING AGING IN POSTMENOPAUSAL WOMEN

In the years during and after the menopause, gonadotropin levels considerably increase (Judd *et al.*, 1978; Rossmanith *et al.*, 1990; Yen, 1991). While aging progresses in the postmenopause, gonadotropin secretion gradually declines, such that gonadotropin levels during senescence almost approximate those of the premenopausal period (Rossmanith *et al.*, 1991b). Fewer LH and FSH secretory episodes with lower pulse amplitudes are observed in aged women, compared with postmenopausal women during their first decade after natural onset of the menopause (Fig. 3). Because the metabolic clearance rates of gonadotropins remain virtually unaffected by age (Kohler *et al.*, 1968), this attenuated gonadotropin pulsatility in old postmenopausal women may indeed relate to decreased gonadotropin release from the pituitary. As gonadotropin pulse frequency primarily reflects intermittent pituitary activation by episodic GnRH release (Knobil, 1980; Clarke and Cummins, 1982), the finding of a lower gonadotropin pulse frequency in aged postmenopausal women may be interpreted as result of a functional decline in the hypothalmic GnRH pulse generator, although a pituitary site of action cannot be entirely excluded (Rossmanith *et al.*, 1991b; Rossmanith 1992a). This notion is further substantiated by the finding of a progressive loss of GnRH neurons at various hypothalamic sites (Witkins, 1989). Moreover, the GnRH content of the hypothalamus has been reported to decrease with advanced age in humans (Parker and Porter, 1984). Thus, our findings suggest a hypothalamic site as the principal cause of the age-related attenuation in gonadotropin secretion. In fact, prolonged estrogen exposure has been demonstrated to decrease the number and functional integrity of hypothalamic GnRH neurons (Brawer *et al.*, 1980), suggesting a pivotal role for ovarian sex steroids in the hypothalamic processes of aging.

The finding of decreased gonadotropin release in postmenopausal women is in keeping with results of some (Judd *et al.*, 1978; Rossmanith *et al.*, 1991b), but not all, previous investigations (Hammond and Ory, 1985; Scaglia *et al.*, 1978). The differences

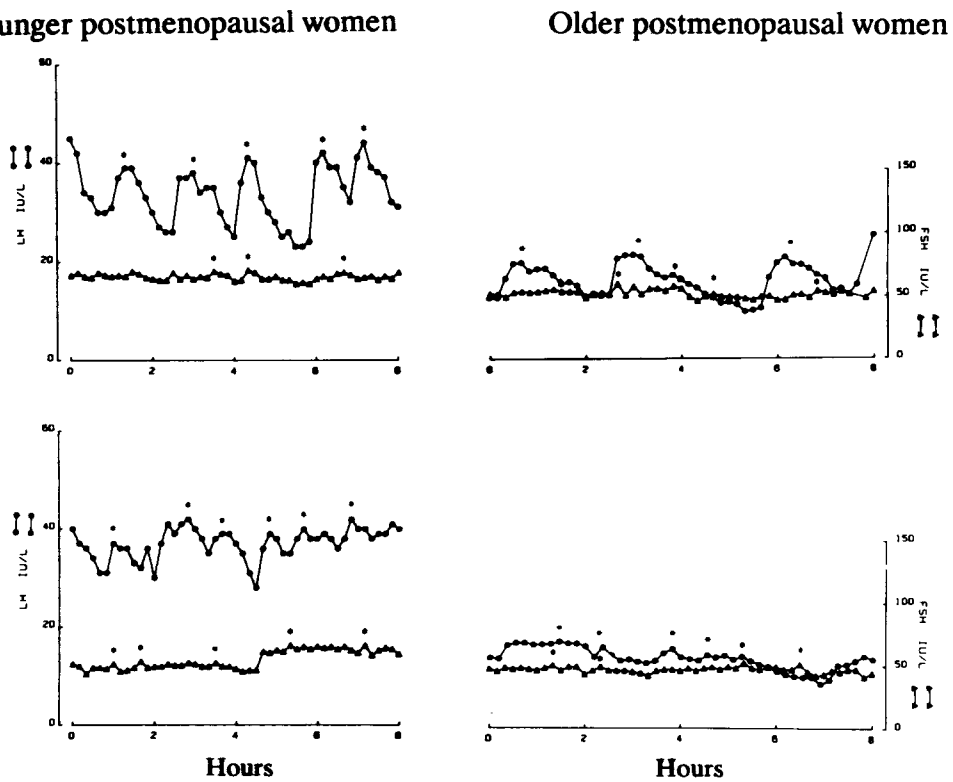

FIG. 3. Representative LH (circles) and FSH (triangles) secretory profiles of two younger (left) and two older postmenopausal women. Asterisks indicate significant pulses (from Rossmanith *et al.* 1991).

may at least partially be reconciled by the heterogeneity of the studied populations. It is well established that concurrent endocrinological and general illness interferes with gonadotropin secretion in postmenopausal women (Morley *et al.*, 1992). Therefore, results obtained in such affected women need to be carefully excluded from analysis, in order not to confound the interpretation. Moreover, the validity of single hormone determinations performed in early studies may be questioned, in view of the marked differences in nadir and peak hormone concentrations (Rossmanith *et al.*, 1991b).

IS PITUITARY GONADOTROPIN RESPONSIVENESS PRESERVED DURING AGING IN POSTMENOPAUSAL WOMEN?

The GnRH-stimulated gonadotropin response has been reported to be clearly exaggerated in postmenopausal subjects compared to premenopausal women (Scaglia *et al.*, 1978). We have conducted an investigation in a large cohort of pre- and postmenopausal women to determine the effects, if any, of advancing age on pituitary gonadotropin responsiveness. GnRH was found to stimulate the LH and FSH secretion during different stages of life in women (Fig. 4). However, when the percentage gonadotropin increments were calculated to take account of variability in basal gonadotropin con-

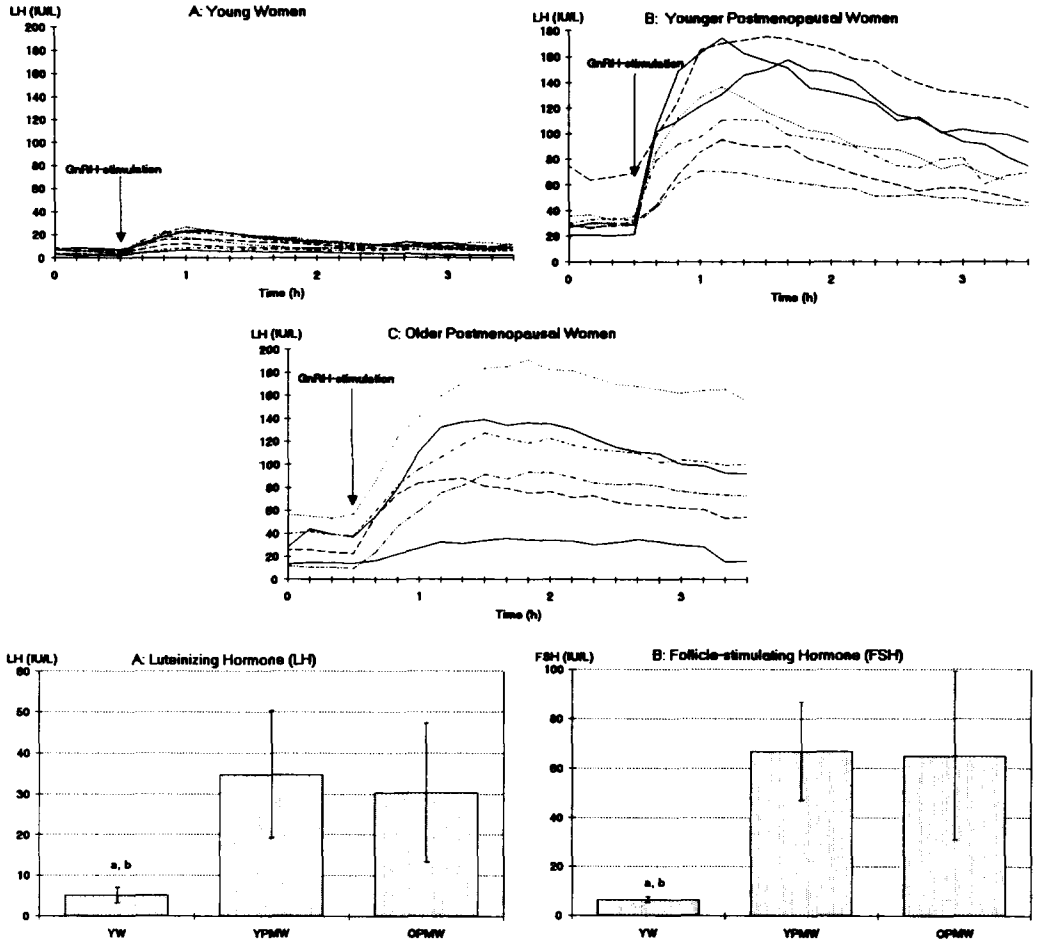

FIG. 4. Individual LH responses to GnRH stimulations (25 μg IV) and relative LH and FSH increments in 9 younger women (mean age: 25.6 years), 7 younger (mean age: 56.6 years) and 6 older postmenopausal women (mean age: 81.9 years). a = $p < 0.01$ versus values of younger PMW, b = $p < 0.05$ versus values of older PMW.

centrations, no differences were found between premenopausal and postmenopausal women even at old age. Thus, the pituitary gonadotroph responsiveness is preserved while aging progresses in women. In particular, it does not vary between postmenopausal women of different ages (Rossmanith *et al.*, 1993). Despite a prolonged period of hypersecretion of gonadotropins in response to low estrogen concentrations in the postmenopause, the pituitary release capacity is apparently not impaired in old women. While earlier studies have claimed a decreased gonadotropin release in response to GnRH stimulation in elderly subjects (Judd *et al.*, 1978), the findings of the current and other investigations (Scaglia *et al.*, 1978; Hanker *et al.*, 1981) are in contrast to this notion. Collectively, pituitary gonadotropin responsiveness is likely to be preserved in old age; this view supports a hypothalamic functional decline as the principal mechanism for the age-related attenuation of gonadotropin secretion in women.

However, it should be remembered that quantitative changes in pituitary hormones may also occur during aging (Wide and Hobson, 1983). The physico-chemical characters of the gonadotropin molecular moieties show an age-related polymorphism. Large LH forms display slower metabolic rates and different biological profiles than the minor ones (Strollo *et al.*, 1981). As deduced from our gonadotropin determinations obtained by radioimmunoassay measurements (Fig. 4), the gonadotropins may be released in response to GnRH stimulation at fairly constant rates throughout pre- and postmenopausal life. In spite of this, the biological potency of these GnRH-stimulated gonadotropins may vary with advancing of age as a result of different distribution patterns in the gonadotropin moieties, and therefore mask the true characteristics of gonadotropin release.

CAN THE FEEDBACK ACTIONS OF OVARIAN SEX STEROIDS STILL BE ACTIVATED IN AGED POSTMENOPAUSAL WOMEN?

It is well established that ovarian sex steroid replacement decreases LH and FSH levels in postmenopausal women (Steger and Peluso, 1987). Because FSH is more sensitive to the negative feedback effects of estrogen than LH (Yen, 1991), factors other than changes in hypothalamic GnRH release have been assumed to account for the differential suppression of these gonadotropins. Estradiol replacement to postmenopausal women does not completely return the FSH serum levels to normal, indicating that additional regulatory components, such as ovarian inhibin, may play a major role for feedback regulation (Morley *et al.*, 1992). Early studies suggested that postmenopausal women may be more responsive to estrogen negative feedback than premenopausal subjects (Yen, 1991). However, this assumption has been questioned, based on the marked differences in the experimental methodologies (Hammond and Ory, 1985). Whether the negative feedback sensitivity of gonadotropins to sex steroid exposure may be relevant to postmenopausal women of advanced age still remains unresolved.

Accordingly, we have used the anti-estrogen clomiphene citrate to probe the gonadotropin sensitivity to negative feedback in postmenopausal women of different ages (Rossmanith *et al.*, 1994b). During the low estrogen milieu of the postmenopause, the anti-estrogen acts as an estrogenic compound. Similar to the gonadotropin suppression previously noted during estradiol replacement therapies (Fig. 2), clomiphene citrate acts as an estrogen to attenuate the gonadotropin secretion in postmenopausal women. In fact, when administered to postmenopausal women during the first decade after onset of the menopause, clomiphene citrate suppressed pulsatile LH and FSH release (Fig. 5). These observations support the concept that the sensitivity of the hypothalamic–pituitary unit to negative feedback may be preserved during the early years of postmenopause (Rossmanith *et al.*, 1994b). In contrast, no such changes in the pulsatile gonadotropin release were noted in aged postmenopausal women, and their pituitary responsiveness remained unaffected by anti-estrogen administration. Therefore, the sensitivity to negative feedback exerted by ovarian sex steroids may be attenuated, or even completely lost, while aging progresses in postmenopausal women. This finding apparently relates to hypothalamic defects rather than to a pituitary functional deficit (Rossmanith *et al.*, 1994b). Recent findings in rodents have suggested an age-associated decline in the sensitivity of the hypothalamus to hormonal feedback

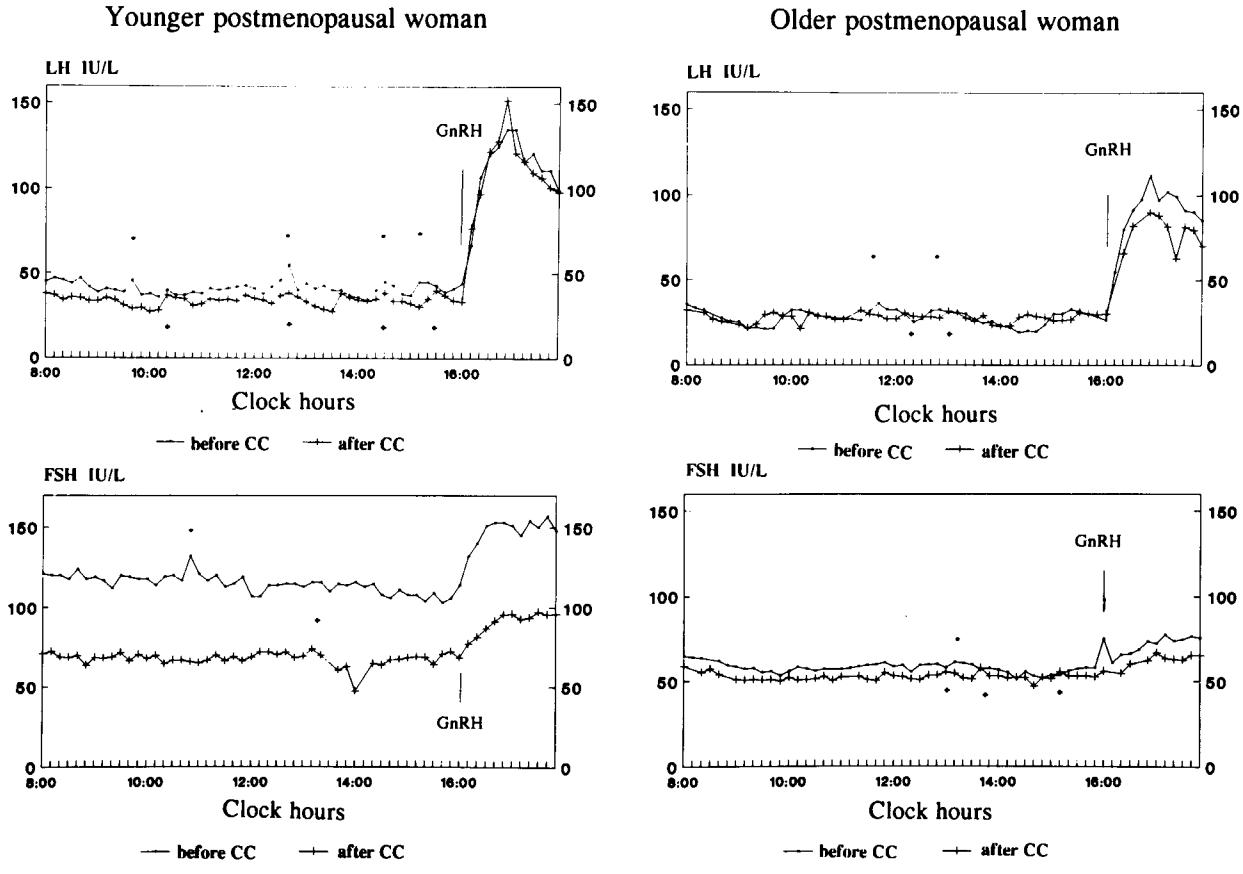

FIG. 5. Unstimulated and GnRH-stimulated LH and FSH secretory profiles of a younger and an older postmenopausal woman before and during administration of clomiphene citrate (CC). *Significant pulses.

(Timiras, 1983), presumably the result of an increased hypothalamic threshold to negative sex steroid feedback. Aging may therefore precipitate a shift in the sensitivity of the hypothalamus to specific hormone actions. Alternatively, the processes of aging may be composed of a discordant pattern in sensitivity changes, during which some of the nuclei become more and others less sensitive to negative hormonal signals (Timiras, 1983).

Feedback effects of the anti-estrogen clomiphene citrate on the hypothalamo-pituitary unit have also been evaluated in aging men. Irrespective of their age, their gonadotropin pulsatility was found to be markedly influenced in response to administration of the anti-estrogen. Combined with our observation of a loss of feedback sensitivity in old postmenopausal women, these findings suggest a sex dimorphism in the age-related affection of the negative feedback control. Relevant to this concept may be the observation that testosterone protects the GnRH neuronal system, quantitatively and functionally, from a decay during biological aging, while prolonged estrogen exposure facilitates the loss of hypothalamic neurons (Finch and Mobbs, 1983).

High doses of estradiol may also induce a positive feedback effect on the gonadotropin secretion in postmenopausal women. A surge-like increase could be elicited by exposing peri- and postmenopausal women to increasing doses of estrogen (Kempers and Ryan, 1977). Whether such positive feedback on the gonadotropin secretion can also be evoked in older postmenopausal women awaits further clarification.

NEUROTRANSMITTER ACTIVITY ON GONADOTROPIN SECRETION DURING AGING IN POSTMENOPAUSAL WOMEN

Imbalanced neurotransmitter control of gonadotropin secretion has been implicated as a possible explanation for age-related functional alterations (Meites, 1988). As implied by the animal model, the hormonal changes associated with aging may not result from a complete loss of transmitter activity, but rather relate to a desynchronization and disorganization of the interrelated neuronal and endocrine signals (Timiras, 1983). Advancing in age does not only influence the effective concentrations of classical neurotransmitters at their target sites in the brain, but may also affect the receptor density and the affinity of neurotransmitters to bind to their receptors (Meites *et al.*, 1982).

Current evidence, although still anecdotal, suggests a selective decrease in the functioning of the monoaminergic neuronal system in humans (Meites *et al.*, 1982). Our evaluation of dopaminergic inhibition on gonadotropin secretion indicates a marked impairment of central dopaminergic activity in postmenopausal women (Rossmanith *et al.*, 1989). In fact, use of a dopamine receptor blocker fails to modify gonadotropin secretory patterns in postmenopausal women. To our knowledge, there are no studies to critically address the possible restoration of dopaminergic inhibitory tone following sex steroid replacement in postmenopausal women. Conversely, gonadotropin secretion in postmenopausal women could effectively be suppressed by administration of dopamine or its agonists (Lachelin *et al.*, 1977). It is therefore suggested that the attenuated dopaminergic activity on gonadotropin secretion found after onset of the menopause may relate, amongst other determinants, to changes in the number and affinity of dopaminergic receptors. Monoaminergic production rates decline, while aging progresses in experimental animals (Meites *et al.*, 1982). Profound alteration have

been found for the dopamine content in the mediobasal hypothalamus (Timiras, 1983) and for dopamine concentrations in the hypothalamo-pituitary portal system (Simpkins and Millard, 1987). Thus, we propose that a decreased central dopaminergic activity may facilitate a self-destruction process, with further derangements in endocrine homeostasis during senescence in women (Hammond and Ory, 1989).

The enhanced gonadotropin levels seen during the postmenopause have been attributed, amongst other factors, to a decline in opioidergic inhibition of gonadotropin secretion. Endogenous opioid activity is absent in postmenopausal women (Reid *et al.*, 1983), but can effectively be restored by estrogen replacement to postmenopausal women (Melis *et al.*, 1988). In turn, dopaminergic activity may mediate effects on the endogenous opioid tone, because administration of a dopamine agonist to postmenopausal women successfully reinstalls the opioidergic inhibition on gonadotropin release (Melis *et al.*, 1984). Collectively, these findings indicate tight functional links between the opioidergic and dopaminergic neuronal systems in postmenopausal women (Rossmanith, 1992b). Thus, combined alterations in the central dopaminergic (Reymond *et al.*, 1989), opioidergic (Melis *et al.*, 1988) and serotoninergic pathways (Hammond and Ory, 1985) may subserve the age-related alterations found in the gonadotropin release of postmenopausal women. Whether derangements in the neurotransmitter activity continue to progress and then account for the profound attenuation of gonadotropin secretion in old postmenopausal women still remains to be elucidated.

CONCLUSIONS

Evidence provided by the current and other investigations has accumulated to suggest that biological aging during the postmenopause markedly affects the neuroendocrine system governing gonadotropin release. The studies presented and their interpretation may aid in expanding our knowledge of the neuroendocrine processes involved in aging. The determination of age-related dynamics in gonadotropin secretion of postmenopausal women has proven to be a valid approach in delineating changes as a function of progressive age. As a result, major functional derangements, primarily at a hypothalamic rather than a pituitary site, have been delineated as concomitants of aging in women. Moreover, aging may also impair the negative feedback sensitivity to ovarian sex steroids, and derangements in central neurotransmitter parallel this decline. By appraising the presented results in relation to neuroendocrine events in the postmenopausal period, we would speculate that the process of aging relates rather to a hypothalamic decline than to a pituitary hypofunction.

While we have made significant advances, our current understanding of the neuroendocrine processes during aging in humans still remains inconclusive. More detailed insights into the complex neuroendocrine alterations during aging may provide better methodologies for the appropriate prevention or attenuation of deleterious effects by specific interventions (Timiras, 1983).

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