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ESTROGEN AND PARKINSON'S DISEASE

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1. ABSTRACT

Female sex hormones, and more specifically estrogen, can have biochemical and behavioral effects on the dopaminergic system. The effects of estrogen on the dopaminergic system can be classified as either neuroprotective or symptomatic. The neuroprotective effects refer to the ability of estrogen to prevent or modulate insults to the dopaminergic system and therefore to alter the natural history of disease processes affecting the dopaminergic circuitry in the brain. With regards to the symptomatic effects, support for both suppressive and enhancing effects has been documented in humans and laboratory animals. The pre-clinical literature for neuroprotective and symptomatic effects of estrogen on the mesostriatal dopaminergic system forms the basis for studies on the influence of estrogen on the prevalence, disease progression, clinical signs, and medication effects of Parkinson's disease and other movement disorders. Understanding the role of estrogen in modulating the dopaminergic system will allow clinicians to tailor therapies for women with Parkinson's disease and optimize therapies for menstrually related symptom fluctuations. Such clarifications may also guide recommendations on the use of postmenopausal hormonal replacement therapy in women with Parkinson's disease or those genetically at risk.

2. INTRODUCTION

The growing awareness of women's health issues in neurology has spawned a focus on the neurochemical modulatory effects of female sex hormones. It is well established that estrogen can modulate the activity of the tubero-infundibular dopaminergic system. Dopamine is released from the tubero-infundibular system into the pituitary portal system and is carried to the anterior pituitary gland, where it acts to inhibit tonically the release of prolactine (1). Estrogen, endogenally secreted or exogenously administered, inhibits the activity of the tuberoinfundibular system, resulting in an increase in prolactin secretion (2). Although the modulatory effects of estrogen on the tubero-infundibular dopaminergic system in the brain are well established, it only recently has become apparent that estrogen can alter the activity of the mesostriatal, mesolimbic and mesocortical dopaminergic systems biochemically and behaviorally (3). However, no consensus has been reached regarding the direction of the effects of estrogen on the dopaminergic system. Support for both suppressive and enhancing effects has been documented in humans and laboratory animals. These conflicting data may be partially explained by differing experimental parameters. In addition to these symptomatic effects, recent evidence indicates that estrogen may exert a neuroprotective influence on the striatal dopaminergic system as well (4).

3. ESTROGEN: PHARMACOLOGY

An estrogen is defined as a natural or synthetic substance that induces estrous (ovulation and mating). Estrogen also promotes the development of ovarian follicles, secondary sexual characteristics, and the female reproductive system, especially proliferation of uterine endometrium and vaginal epithelium. Estrogens can be categorized as natural steroidal, synthetic steroidal, and non-steroidal (5). Natural steroidal estrogens include estrone (E^1), 17-alpha-estradiol, 17-beta-estradiol (E^2), estriol (E^3), equilin, and equilenin (figure 1). They are C-18 steroids with a phenol A ring and various hydroxyl or ketone groups. Synthetic steroidal estrogens often have side groups to improve potency and duration of action.

Oral estrogen is subjected to the first-pass effect through the liver, where they are metabolized. The liver also binds estrogen to plasma proteins, and inactivates estrogen by conjugation with glucuronic acid or sulfate to form water-soluble compounds that are excreted in the urine. Estrogen is available as oral, transdermal, intravaginal, and intramuscular preparations (6). Parenteral routes of administration avoid the first pass effect through

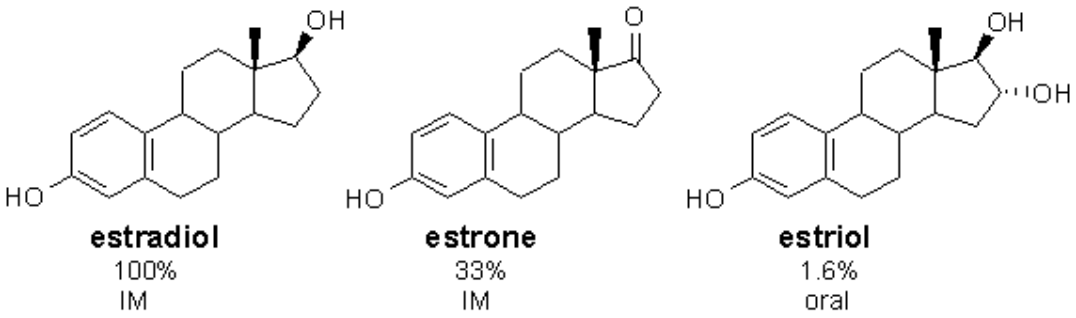

Figure 1. Natural estrogens. Although estradiol is the most active with 100% activity, the advantage of estriol is that it can be taken orally

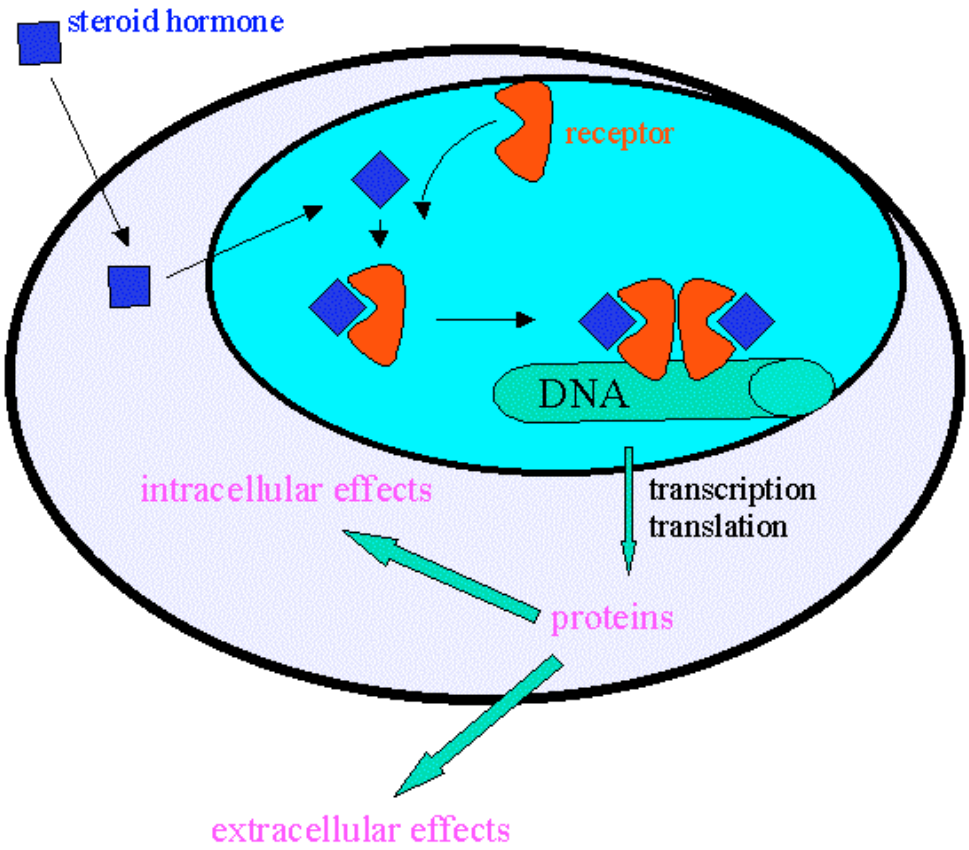

Figure 2. Genomic mechanism of action of estrogens through nuclear receptors

the liver. Currently available preparations include conjugated equine estrogens (Premarin), esterified estrogen (Ogen, Ortho-est), micronized estradiol (Estrace), transdermal estradiol (Estraderm, Climara). As long as appropriate doses are used, there is no advantage of one form over another form of estrogen (7).

4. ESTROGEN AND THE BASAL GANGLIA

4.1. Neuroprotective Effects of Estrogen on the Dopaminergic System

Estrogen administration significantly attenuates the degree of striatal dopamine depletion to neurotoxins, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA) and methamphetamine, which target the nigrostriatal dopaminergic system (8). This neuroprotection appears maximal with the 17 beta-isomer as opposed to the 17 alpha-isomer (9, 10) and in some experiments specific to female, but not male rats (11).

In vitro, estrogen protects neuronal PC12 cells (12), mesencephalic neurons (13), and striatal neurons (14) from toxicity induced by MPTP or 6-OHDA. Furthermore, 17 beta-estradiol protects lymphocytes against dopamine and iron-induced apoptosis (15). *In vivo*, estrogen-treated animals sustain less dopamine depletion in the striatum following administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (4, 9-11, 16-20) or

methamphetamine (17, 21). More specifically, estradiol can protect striatal dopamine neurons against MPP^+ toxicity by decreasing the immediate dopamine release occurring in response to this neurotoxin (22). The neuroprotective effect of estrogen on the dopaminergic system is abolished in the presence of tamoxifen, a potent anti-estrogen compound (20).

Despite the data showing the neuroprotective effects of estrogen with regard to the dopaminergic system, little is known about the mechanisms and cellular targets by which estrogen might elicit its protective influence. Studies on developing midbrain dopaminergic neurons have revealed that estrogen is an important regulator of plasticity and function of this neuronal phenotype (23). Dopaminergic neurons are direct targets for estrogen and estrogen stimulates neurite extension/branching and the expression of tyrosine hydroxylase (23). The presence of the estrogen-synthesizing enzyme aromatase within the nigrostriatal system further supports the idea that estrogen is required for the plasticity and activity of the developing and adult nigrostriatal system.

Finally, besides regulating dopaminergic neuronal plasticity and neurite extension/branching, other putative mechanisms of neuroprotection have been suggested in the literature. Estrogen has been proposed to possess antiapoptotic activity (24), to have antioxidant action (13, 15), to be involved in neurotrophic cross talk through the signal cascade shared with neurotrophic factors (25), and to influence the activity of the dopamine transporter (8, 14, 26), thus preventing neurotoxic agents from entering dopamine nerve terminals.

4.2. Symptomatic Effects of Estrogen on the Dopaminergic System

Estrogen effects on the nigrostriatal cell function are transmitted by genomic mechanisms, through classical nuclear receptors (figure 2), but also through non-genomic mechanisms, mediated by putative membrane receptors coupled to diverse intracellular signaling cascades (24). For example, estrogen can interact with membrane binding sites on dopaminergic neurons, thereby stimulating the cAMP/PKA/phosphorylated cAMP-responsive element binding protein (CREB) signaling cascade, most likely through activation of protein kinases (27). In regards to the genomic mechanisms, although there is a paucity of intracellular estrogen receptors-alpha in the substantia nigra and the ventral tegmental area, the newly described beta isoform of the estrogen receptor is found in a relative abundance (28). It has been suggested that in the midbrain, genomic and non-genomic signaling routes operate side by side to ensure the proper development of dopaminergic cells (29).

Data from both clinical and animal research clearly indicate that estrogen affects the dopaminergic system at the neurochemical level, as well as the behaviors mediated by striatal dopamine. However, there is controversy concerning whether estrogen enhances or suppresses the striatal dopaminergic system, as well as the mechanisms by which it might produce these effects. Selected data suggesting estrogen-related enhanced and suppressed dopaminergic activity are listed in Tables 1 and 2, and discussed below. Factors that may account for these contradictory data are: the dose of estrogen, the time interval between estrogen administration and experimental measurement, sex differences, time interval after ovariectomy, estrogen status of the host, strain differences, age of the animal, dose of dopamine agonist used to elicit a stereotyped behavior, time of the day the experiment is performed, and method of measuring the behavior (3). Estrogen may have different effects on manipulations involving pre- versus postsynaptic elements of the striatal system, different actions on the mesostriatal, mesolimbic, and mesocortical systems respectively, and direct versus indirect effects.

An alternative hypothesis concerning the effects of estrogen on behaviors mediated by striatal dopamine systems is that these effects may be indirect. Whether given exogenously or occurring endogenously, an increase in estrogen is typically followed by an increase in its own metabolites, particularly the catechol estrogens and by a prolactin surge (3). In the tubero-infundibular system, prolactin has effects opposite to those of estrogen. In the mesostriatal system, it is thought to mediate the effects of estrogen on apomorphine-induced behaviors and the delayed increase in striatal dopamine receptors following a dose of estrogen. More specifically, hyperprolactinemia enhances dopamine agonist-induced stereotyped behavior (30, 31), and attenuates catalepsy (32).

In the intact animal, following estrogen administration, a progesterone surge is also seen (3). During the estrous cycle, the progesterone surge follows the estrogen surge, and therefore, the various changes in biochemistry and behavior that take place between proestrous and estrous are difficult to ascribe to estrogen with certainty. Progesterone has not been systematically studied, and hence its role is as controversial as that of estrogen. Some authors find it to be antagonistic to the activity of estrogen with respect to the dopaminergic system (33-35), others report synergism (36-38), and others report no effect (39, 40).

In reference to the time interval between estrogen administration and drug-elicited stereotyped behavior in experimental animals, Gordon *et al* (41) suggested that administration of a large dose of estrogen results in a biphasic behavioral effect with an early phase corresponding to suppression and a later phase corresponding to enhancement of dopaminergic activity. Lower doses of estrogen lead to a short-term suppression of dopamine mediated behaviors without a delayed enhancement (41). At the postsynaptic level, estrogen treatment increases the density of dopamine D2 receptors in the striatum (42). Because estrogen initially antagonizes presynaptic measures of striatal dopamine activity, it is thought that the delayed changes in dopamine receptor number might represent a compensatory postsynaptic change. These results suggest that estrogen can mimic some of the actions of neuroleptics, i.e. producing supersensitive dopamine receptors upon withdrawal as well

Table 1. Pro-dopaminergic Effects of Estrogen on the Mesostriatal Dopaminergic System

Histology/ Biochemistry	Behavior	Species	Gender	Estrogen formulation	Reference
Increase in TH activity		Rat	OVX females	17_-estradiol	44
Increase in HVA and DOPAC	Induction of postural deviation to the site of entopeduncular nucleus lesion	Rat	OVX females	17_-estradiol	45
Increase in basal and K^+-stimulated DA release		Mouse	OVX females CAST males	Estradiol benzoate	51
Increase in AMPH-stimulated striatal DA release in vitro	Increase in rotational behavior in 6-OHDA lesioned rats	Rat	OVX females	Estradiol benzoate	47
Inhibition of DAT activity		Rat	OVX females	17_-estradiol	22
Down-regulation of MAO activity		Rat	Across estrous		53
Down-regulation of COMT activity				17_-estradiol	54
Increase in DA receptor density	Increased duration of AMPH-induced rotation in 6-OHDA lesioned rats	Rats	Intact males	Estrogen	50
Increase in DA receptor binding sites		Rats	OVX females	17_-estradiol	42

TH: tyrosine hydroxylase; OVX: ovariectomized; HVA: homovalinic acid; DOPAC: 3,4-dihydroxyphenylacetic acid; DA: dopamine; CAST: castrated; AMPH: amphetamine; 6-OHDA: 6-hydroxydopamine; DAT: dopamine transporter; MAO: monoamino oxidase; COMT: catechol-O-methyltransferaseas shifting the dose response curve for apomorphine in a direction consistent with a blockade of dopamine receptors. This observation may underlie the higher association of tardive dyskinesia among women.

Studies utilizing the systemic administration of dopaminergic agonists and dopamine antagonists cannot control for the peripheral effects of estrogen such as altered drug metabolism or differences in drug uptake into the brain (43). However, one group of investigators reported that estrogen administration failed to increase blood or brain levels of either 3H-amphetamine or 3H-apomorphine suggesting that its behavioral effects were not due to altered peripheral drug metabolism or uptake into the brain (43).

4.2.1. Pro-dopaminergic Effect of Estrogen on the Dopaminergic System

At the symptomatic level, several studies support the role of estrogen as a facilitator of dopaminergic function (table 1). When male or ovariectomized female animals are treated with estradiol, enhancement is seen in the synthesis, metabolism, and release of dopamine in the striatum as well as the dopamine receptor density (44-50). Following estradiol treatment, there is increase in tyrosine hydroxylase activity (44) and in the dopamine metabolites, homovanillic acid and dihydroxyphenylacetic acid (45). Estrogen potentiates both basal and potassium-stimulated dopamine release from female mouse striatum when superfused in vitro (51) and increases amphetamine-stimulated dopamine release and rotational behavior in 6-hydroxydopamine lesioned rats (47). In non-human primates, ovariectomy decreases the density of dopamine neurons and the number of tyrosine hydroxylase-expressing neurons in substantia nigra pars compacta. This dopaminergic cell loss is reversed by brief estrogen replacement after 10 days but not after 30 days following ovariectomy (52).

Possible mechanisms by which estrogen exerts its modulatory effect on the dopaminergic system include inhibition of the dopamine transporter activity (22), down-regulation of monoamino oxidase (MAO) activity (53), or down-regulation of catechol-O-methyltransferase (COMT) activity (54). At the post-synaptic level, estrogen treatment increases the density of dopamine receptors (48-50).

4.2.2. Anti-dopaminergic Effects of Estrogen on the Dopaminergic System

In spite of the above evidence, there is an extensive body of literature supporting antidopaminergic effects of estrogen, in particular affecting dopaminergic receptors supersensitivity (table 2). Pretreatment with 17_-estradiol reduces the dyskinetic effect of levodopa in cynomolgus monkeys (55). Estrogen abolishes the haloperidol-induced rebound late supersensitivity to apomorphine in a dyskinetic monkey model. Late hypersensitivity to apomorphine, occurring on day 15 after single intramuscular injection of haloperidol, follows initial suppression of the apomorphine response in this dyskinetic monkey model (56). Female rats during their reproductive years have fewer striatal dopamine receptors than male rats and this number is further reduced with estradiol treatment. Furthermore, female rats exhibit lower apomorphine-induced stereotypy during phases of their cycle with high estrogen levels (57). Estradiol benzoate treatment of ovariectomized rats suppresses unilateral intrastriatal dopamine-induced postural deviation (58). Moxestrol, a synthetic estrogen antagonizes the contralateral circling elicited by apomorphine in unilaterally 6-hydroxydopamine lesioned rats and blocks the apomorphine-induced increase

Table 2. Anti-dopaminergic Effects of Estrogen on the Mesostriatal Dopaminergic System

Histology/ Biochemistry	Behavior	Species	Gender	Estrogen formulation	Reference
	Decrease of L-dopa-induced dyskinesia in MPTP-treated monkeys	Monkey		17_-estradiol	55
	Decrease in haloperidol-induced late supersensitivity to APO in a dyskinetic monkey model	Monkey	OVX females	Estradiol benzoate	56
Decrease in DA receptors in cycling female rats than male rats, and this number is further reduced by estradiol treatment	Lower APO-induced stereotypy during cycle phases with high estrogen levels	Rat	Cycling and OVX females Intact males	17_-estradiol	57
	Decrease in unilateral intrastriatal DA-induced postural deviation	Rat	OVX females	Estradiol benzoate	58
	Decrease in APO-elicited contralateral circling in unilaterally 6-OHDA lesioned rats	Rat	Intact males CAST males OVX females	Moxestrol	59 61
	Decrease in APO-elicited contralateral circling in rats with unilateral entopeduncular nucleus lesion	Rat	OVX females	Estradiol benzoate	
	Decrease in APO-induced stereotypy	Rat	OVX females	Estradiol benzoate	62
Decrease in DA concentration in the striatum		Rat	OVX females	17_-estradiol	63
	Increase in spiperone-induced catalepsy	Rat	OVX females	Estradiol benzoate	64

MPTP: 1-mehtyl-4-phenyl-1, 2,3,6-tetrahydropyridine; DA: dopamine; APO: apomorphine; OVX: ovariectomized; 6-OHDA: 6-hydroxydopamine; CAST: castrated

in striatal acetylcholine (59, 60). Estradiol treatment decreases the apomorphine-induced circling in rats with lesions of the entopeduncular nucleus (61). Large estradiol doses attenuate apomorphine-induced stereotypy in the rat (62). Chronic estrogen treatment in ovariectomized rats decreases dopamine concentration in the striatum (63). Finally, estradiol benzoate increases spiperone-induced catalepsy in the rat (64).

5. ESTROGEN AND PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disorder characterized by loss of melanin-containing neurons in the substantia nigra pars compacta, the presence of Lewy bodies, and a reduction of striatal dopamine (65). The disease has a mean age of onset of 50 to 60 years (66), but both its incidence and prevalence increase steadily with age (67). The prevalence of Parkinson's disease in North America has been estimated to range from 100 to 187 per 100,000, per year (67). All of the above numbers are expected to rise with the growing elderly population. Parkinson's incidence is higher in men than in women (68-77) but because of their greater longevity, women constitute an increasing percentage of the Parkinson's disease prevalence.

Post-menopausal estrogen replacement therapy has been associated with a reduced risk of Parkinson's disease in women (78), and estrogen replacement therapy exposure is associated with delayed age of onset of Parkinson's disease (79). Nursing home residents carrying the diagnosis of Parkinson's disease and taking estrogen have been found to be less cognitively impaired and more independent in their activities of daily living compared to non-estrogen users, independent of age (80). More direct evidence suggests that there is a positive association between estrogen replacement therapy use and lower disease severity in women with early Parkinson's disease who are not on levodopa (81). Finally, estrogen replacement therapy supplementation has been reported to improve Parkinson's disease symptoms (82), while estrogen replacement therapy withdrawal increases motor impairment (82, 83).

The primary clinical signs of Parkinson's disease are tremor, rigidity, bradykinesia, and poor postural reflex function. In non-parkinsonian elderly women, postural balance function is better preserved in those who use long-term estrogen replacement therapy than in non-users (84). Parkinsonism induced by neuroleptic medications, drugs that block dopamine receptors, occurs more frequently in women and particularly post-menopausal women (85).

In addition to the cardinal features of Parkinson's disease, after several months or years of dopaminergic drug

replacement therapy, patients develop involuntary movements termed dyskinesias. Women with Parkinson's disease have been found to be more prone than men to the development of levodopa-induced dyskinesias (86). This observation raises questions about the effects of endogenous or exogenously administered estrogen on the central utilization of levodopa. A recent double-blind, placebo-controlled, two arm, cross-over pilot study assessed the short-term effects of high dose transdermal 17-estradiol on the response profile to intravenous boluses of levodopa. Transdermal 17-estradiol significantly decreased intravenous levodopa antiparkinsonian response threshold without altering dyskinesias, demonstrating estrogen-induced enhancement of dopaminergic function (87).

Motor fluctuations are another complication of long term treatment with levodopa. In a study of 40 post-menopausal women with Parkinson's disease and motor fluctuations, low estrogen supplementation was found to improve "on" time, "off" time and motor score measured with the Unified Parkinson's Disease Parkinson's Scale (UPDRS) (88).

Menstruating women with Parkinson's disease experience cyclic changes of their parkinsonism, with premenstrual worsening coinciding with a nadir in both estrogen and progesterone levels (89-94). Specifically, premenstrual deterioration with loss of medication efficacy has been reported in 25% of menstruating women with Parkinson's disease (95). Other studies have failed to reproduce these results. Specifically in a study designed to correlate motor signs with hormonal levels, the authors prospectively studied 10 menstruating women with PD in their "off" state, on 5 successive weeks. Although PD severity fluctuated during the study period, there was no significant correlation between the objective or subjective measures of parkinsonism and estrogen and progesterone levels (89).

In non-placebo controlled studies, estrogen replacement therapy is protective for the development of dementia within the setting of Parkinson's disease (96). A history of estrogen replacement therapy supplementation is associated with better performance in the Mini-Mental Status Exam (MMSE) (97) and better verbal memory retention (98) in parkinsonian women.

In summary, it appears that estrogen may play a favorable role as to the development of Parkinson's disease as well as the severity of motoric symptoms, the occurrence and severity of motor complications, and the cognitive function of women with PD.

6. CONCLUSIONS AND PERSPECTIVES

Data from both clinical and animal research clearly indicate that estrogen affects the neurochemistry of dopamine as well as behaviors mediated by dopamine. Further elucidation of the mechanism by which estrogen affects the dopaminergic system will clarify the conflicting evidence as to the direction of this effect. Similar considerations apply to the serotonergic, noradrenergic, and cholinergic systems.

Estrogen effects on dopamine and other neurotransmitters may explain gender differences in the natural prevalence of movement disorders. A clearer understanding of the role of estrogen on Parkinson's disease will allow a better clinical approach to treating symptom fluctuations during the menstrual cycle, better care of postmenopausal women with movement disorders, and insight into possible prevention of disease development or progression. Whereas the age at which menopause starts has remained stable across the past century, female life expectancy has risen continuously and dramatically over the same period of time. At the present time, women can expect to live almost one-third of their lives after menopause (99). Therefore, a major goal of preventive medicine is to extend the duration of functional well being and, if possible, to retard the progression of chronic illnesses once they have emerged.

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