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Estrogen as Neuroprotectant of Nigrostriatal Dopaminergic System

Laboratory and Clinical Studies

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In this review, we relate both laboratory and clinical evidence associated with the capacity for estrogen to function as a modulator of nigrostriatal dopaminergic pathology. To accomplish this goal, we have divided this review into three parts. In Part 1, we provide a brief historical perspective of studies that have laid the groundwork for demonstrating the existence of hormonal-nigrostriatal interactions. In Part 2, we focus specifically on laboratory data that show the ability and conditions by which estrogen may function as a neuroprotectant of the nigrostriatal dopaminergic system. Finally, in Part 3, we review the clinical literature related to this issue as a means for consideration of estrogen as a modulator, neuroprotectant, and therapy for Parkinson disease.

Key Words: Parkinson disease; gonadal steroids; progesterone; testosterone; neurodegeneration; dopamine.

Introduction

This review is divided into three parts related to the issue of estrogen's ability to serve as a neuroprotectant of the nigrostriatal dopaminergic (NSDA) system. Because we all too often become enamored with our own work and convince ourselves of the landmark nature of our findings, in Part 1 we attempt to put this issue into a historical perspective. Accordingly, we present a description that traces the evolution of significant findings that have laid the groundwork for the hypothesis that estrogen can function as an NSDA neuroprotectant. In Part 2, we review the data that show the conditions and characteristics for estrogen to exert neuroprotection on the NSDA system as derived from laboratory experiments. Finally, because the ultimate goal of this basic research is the extrapolation and application to clinical conditions, in Part 3 we endeavor to relate these laboratory findings to data from the clinical literature as associated with estrogen and Parkinson disease.

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Part 1: A Brief History

Gonadal Steroids and the NSDA System

Tracing back through the literature to identify the foundation for recognizing estrogen's capacity to function as a neuroprotectant of the NSDA system reveals a number of significant findings that have successively built on each other. The most basic and critical of these steps involved a demonstration that gonadal steroid hormones can influence NSDA function. One of the first indications that the NSDA system may be influenced by gonadal steroid hormones was reported in 1969 by Lichtensteiger *(1)*. Lichtensteiger was primarily interested in hypothalamic catecholamine content variations across the estrous cycle of the rat but included samples from the substantia nigra for comparison. Although it received little attention and discussion, significant changes in substantia nigra catecholamines were observed in this report. A more direct, but less anatomically refined, examination of this issue followed in 1971 by Greengrass and Tonge *(2)*, who reported dopamine (DA) concentration changes as a function of the estrous cycle. However, these changes were obtained from samples of a "midbrain" area that included the hypothalamus, thalamus, and striatum, making it difficult to pinpoint the exact system involved. Shortly after this report, in 1973, it was demonstrated that estrous cycle changes in homovanillic acid levels *(3)* and monoamine oxidase activity *(4)* were present within the striatum. These data indicated a more direct effect within the NSDA system but were based on indirect indices of dopaminergic activity within the striatum. A more definitive demonstration of estrous cycle variations in striatal dopaminergic functions resulted from data presented in the mid- to late 1970s that showed changes in DA turnover *(5)* and DA concentrations *(5,6)*. Now a clear effect of gonadal steroids on striatal DA was established. Such findings have received support from a variety of sources, and, currently, estrous cycle differences have been confirmed for a range of NSDA functions including DA turnover rates *(5,7)*, DA release *(5–12)*, DA D-1 and

D-2 binding sites *(13,14)*, DA uptake *(15,16)*, striatal dendritic morphology *(17)*, amphetamine-stimulated behavior *(18)*, sensorimotor behavior *(19)*, and behavioral responses to DA agonists and antagonists *(20)*.

With the evolution of these initial landmark studies and their subsequent confirmation, the capacity for gonadal steroids to modulate an extrahypothalamic site, specifically the NSDA system, was authenticated. The significance of these findings was not merely limited to the basic demonstration of an effect of gonadal steroids on NSDA function. Of equal importance was the opening of two related avenues of inquiry regarding influences of gonadal steroid hormones on the NSDA system: (1) the potential for gender differences in NSDA function, and (2) the identification of the precise female gonadal steroid hormone (estrogen and/or progesterone) involved in this estrous cycle modulation.

Gender Differences and the NSDA System

Regarding gender variations, significant differences in striatal DA concentrations, along with greater locomotor activity responses (females > males), were initially reported almost 30 yr ago by Gordon and Shellenberger *(21)*. They described a positive correlation between spontaneous motor activity and striatal DA. Of significance to this review was their data showing greater spontaneous and wheel-running activity along with greater striatal DA concentrations within their control female vs male rats. Approximately 4 yr after this initial article, a second article confirmed the existence of gender differences in striatal DA concentrations—however, in an opposite direction (females < males) *(22)*. Since neither article specified the estrous cycle day on which the females were sampled, this factor may provide an explanation for dissimilarities in the direction of the gender dissimilarities. A number of reports on this topic followed over subsequent years, and what can be concluded, as based on a review of this topic, is that clear gender differences characterize functioning of the NSDA system *(23)*.

Estrogen-Progesterone and the NSDA System

Interestingly, the initial work involved in identifying the specific gonadal steroid hormone responsible for modulating NSDA activity surfaced from clinical articles more than 40 yr ago. The observation that administration of estrogen resulted in the display of extrapyramidal/parkinsonian-like symptoms in patients treated with neuroleptics was clearly suggestive of an estrogen-dependent modulatory effect on NSDA functioning *(24)*. A number of case studies have reported similar findings, providing support for the belief that estrogen can exert modulatory effects on the NSDA system *(25–27)*. Approximately 12 yr after this initial clinical observation, one of the first laboratory studies was conducted to examine this issue *(28)*. Analogous to that observed clinically, the administration of estrogen potentiated amphetamine-induced stereotypy in rats. The results were confirmed in a subsequent study and extended to demonstrate that progesterone could also exert an enhancement of this amphetamine (or apomorphine)-induced stereotypy in rats *(29)*. With the start of the 1980s, a series of neurochemical and biochemical determinations were employed to supplement these behavioral assay data in confirming that the NSDA system did represent an important target site for modulation by estrogen and/or progesterone *(30–32)*.

In contrast to that of the female, substantially less information is available on the potential for testosterone to exert modulatory effects within the NSDA system of the male. One of the first attempts to examine this issue involved measuring caudate nucleus DA concentrations between male rats subjected to either sham or neonatal castration *(22)*. The results from this study were negative in that virtually identical adult DA concentrations were obtained between the sham and neonatally castrated males. By contrast, data from behavioral assays revealed that testosterone attenuated the effects of amphetamine on locomotor activity and stereotypy *(33–35)*, suggesting a modulatory effect on the NSDA system. A clear effect of testosterone on the NSDA system was confirmed with the demonstration that castrated male rats show increased locomotor activity associated with increased striatal DA release, while testosterone treatment returns these DA release rates back to levels observed within intact males *(36)*.

Conclusion

We have highlighted some of the initial studies that have laid the foundation demonstrating that an extrahypothalamic area could represent an important target site for gonadal steroid hormones. Such findings have wide-ranging implications because they suggest a basis for estrous/menstrual cycle and gender differences in the functioning of this system. The fact that this site was the NSDA system insinuates the presence of an important connection between gonadal steroid hormones and movement disorders. When this connection is combined with data showing that estrogen can alter the display of extrapyramidal/parkinsonism-like symptoms and the suggestion of a gender difference in Parkinson disease, the creation of the hypothesis that gonadal steroids may modulate the pathology of the NSDA system is realized.

Part 2: Gonadal Steroids and the NSDA System—Neuroprotection

Gender Differences and NSDA Neuroprotection

The identification of gender differences in NSDA function, which can be seen to be attributable to gonadal steroids, stimulated a plethora of research on this topic *(23,30,31)*. While gender differences in NSDA functioning have several consequences, of particular significance to the present review are the data that indicate that these gender/gonadal steroid hormone variables affect the neurotoxicity and neurodegeneration of the NSDA system. In 1989, Brooke et al. *(37)* were the first to demonstrate a gender difference in

NSDA neurotoxicity. They treated female and male mice with varying doses of the NSDA neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and found that the amount of striatal DA depletions were greater in males. This gender difference in response to MPTP treatment was confirmed by independent laboratories *(38–40)* and was also seen following treatment with a neurotoxic regimen of the psychostimulant methamphetamine *(41–44)*. Accordingly, the results obtained from these studies expanded the realm of gender differences in NSDA function to encompass neurodegeneration. What these data lacked were the identification of specific gonadal steroid hormones involved in this phenomenon and a sense of whether these gender differences were attributable to increased susceptibility in males, decreased susceptibility in females, or a combination.

Estrogen-Progesterone and NSDA Neuroprotection—Females

One of the first hints of a potential interaction among estrogen, striatal dopaminergic activity, and MPTP was indicated by Bedard's laboratory, which reported that ovariectomized (OVX) female monkeys treated with MPTP showed significantly reduced L-dopa-induced dyskinesias when treated with 17β-estradiol, but not 17α-estradiol or progesterone *(45)*. Since the MPTP was administered prior to the estrogen in this study, it cannot be determined how the estrogen may be interacting with this neurotoxin because the MPTP-induced neurodegeneration was already present on application of the estrogen.

In an attempt to examine specifically the effects of estrogen on MPTP-induced NSDA neurotoxicity, we performed a simple experiment in which OVX mice treated or not with estrogen received MPTP *(46,47)*. Mice pretreated with estrogen prior to MPTP administration had significantly greater striatal DA concentrations when assayed at 1 wk post-MPTP. This suggested that estrogen could serve as a neuroprotectant against a toxin that targets the NSDA system. This protection against MPTP-induced neurotoxicity of the NSDA system by estrogen in OVX mice was supported by data presented from others *(40)*. Moreover, this estrogen-dependent protection was shown to occur against other NSDA neurotoxins including 6-OHDA *(48)* and methamphetamine *(43, 49–51)*. These neuroprotective effects of estrogen show a stereospecificity because only the 17β-estradiol, not the 17α-estradiol, isomer was effective in producing a significant neuroprotective action *(52,53)*. The potential for these estrogen effects on neuroprotection to represent physiologic responses has been indicated from data showing that estrous cycle differences are present to methamphetamine-induced NSDA neurotoxicity *(43)* and that serum levels of estradiol in estrogen-treated mice demonstrating neuroprotection are within the range of physiologic levels *(49)*. These effects of estrogen on neuroprotection can be demonstrated to represent a rapid, acute mechanism of estrogen action since administration at 24, 12, and even 0.5 h prior to methamphetamine results in a preservation of NSDA function *(54)*. However, estrogen treatment after methamphetamine insult fails to offer any prevention of striatal DA depletion when tested both acutely (0.25–2 h postmethamphetamine *(54)* as well as at 1 wk postmethamphetamine *(49)*. Nor can estrogen function as a neuroprotectant against methamphetamine-induced NSDA neurotoxicity in female mice gonadectomized prepubertally *(55,56)*. In this way, estrogen can be seen to require both organizational effects on the NSDA system at the pubertal period to exert its subsequent activational effects on NSDA neuroprotection in the adult.

The effectiveness of estrogen to work as a neuroprotectant of the NSDA system raises the question, What are the effects of the antiestrogen, tamoxifen? Tamoxifen treatment produced some complex expected and unexpected results regarding NSDA neurotoxicity. In OVX mice treated with a combination of estrogen and tamoxifen, the neuroprotection afforded by estrogen was abolished when tested with both MPTP- *(53)* and methamphetamine *(49)*-induced neurotoxicity. This abolition was not seen when estrogen was administered simultaneously with the active metabolite of tamoxifen, 4-hydroxytamoxifen *(55)*. In fact, striatal DA concentrations in these estrogen + 4-hydroxytamoxifen–treated OVX mice following methamphetamine were not only significantly greater than in mice receiving vehicle, but also greater than in those mice treated with estrogen alone. The other unexpected finding was that tamoxifen administration to intact female or male mice seemed to function as a neuroprotectant with striatal DA concentrations of these mice being significantly greater than nontamoxifen-treated mice receiving methamphetamine *(57)*. Accordingly, when administered to intact mice and/or OVX mice with a specific amount of estrogen treatment, tamoxifen appears to function as an agonist or a potentiator of NSDA neuroprotection, an effect that is also present in male mice.

The issue of whether the other female gonadal steroid, progesterone, can offer any neuroprotective characteristics has received much less attention. The limited data available indicate that progesterone alone *(52)* as well as in combination with estrogen priming can also serve as a neuroprotectant of the NSDA system against MPTP- and methamphetamine-induced neurotoxicity *(52,58)*. However, this progesterone effect may not be as robust as that of estrogen *(55)*. Other related compounds that show a neuroprotective effect like that observed with estrogen include the nonsteroidal selective estrogen receptor modulator raloxifene *(52)* and dehydroepiandrosterone *(59)*.

Estrogen-Progesterone and NSDA Neuroprotection—Males

The gender differences observed in response to NSDA neurotoxins and associated data showing that estrogen, as well as progesterone, represent likely candidates for the basis of this neuroprotection beg the question: Could these gonadal steroid hormones function as neuroprotectants within

the male? There appears to be an interesting neurotoxin specificity regarding estrogen's capacity to function as a neuroprotectant within the male mouse. When the NSDA neurotoxin MPTP was used as the agent to induce striatal DA neurodegeneration, estrogen could function as an effective neuroprotectant *(47,52)*. However, when estrogen was tested for its neuroprotectant ability within male mice receiving methamphetamine, no evidence for neuroprotection was obtained *(51,55,60)*. The discriminatory ability of estrogen to function as a neuroprotectant to MPTP, but not methamphetamine, within male, but not female, mice offers a potentially useful model to exploit in order to understand the interaction among gender, estrogen, and NSDA neurotoxicity. Unlike that seen for estrogen, progesterone is capable of producing a robust neuroprotective effect within male mice treated with MPTP *(52)* or methamphetamine *(55)*. A description of potential mechanisms by which estrogen can exert this neuroprotective effect on neurotoxins that target the NSDA system is provided in a number of recently published reviews *(50,51,61–63)*.

Testosterone and NSDA Neuroprotection

While the presence of estrogen and progesterone may play a critical role regarding the gender differences in NSDA neurotoxicity, a complementary issue requiring consideration is whether the predominantly male gonadal steroid hormone, testosterone, can alter neurodegeneration within the NSDA system. There are some indications that testosterone may actually enhance NSDA neurodegeneration, although the data are not solid. L-Dopa-evoked DA release from superfused striatal tissue of orchidectomized testosterone-treated CD-1 mice was significantly reduced following treatment with MPTP. No differences in L-dopa-evoked DA release between orchidectomized mice treated or not with testosterone were obtained following treatment with the vehicle for MPTP *(64)*. Moreover, striatal DA concentrations are consistently lower, albeit not always statistically significant, in testosterone- vs vehicle-treated rodents following methamphetamine *(51,56)* or 1-methyl-4-phenyl-pyridine+ treatment *(59)*. What can be stated with certainty is that testosterone offers no neuroprotection, since striatal DA concentrations of testosterone- or dihydrotestosterone-treated animals are at, or more likely below, that obtained in vehicle controls following MPTP or methamphetamine treatment *(60,65,66)*.

Conclusion

We have presented laboratory data demonstrating the capacity and conditions under which gonadal steroid hormones can modulate NSDA neurodegeneration. A summary of these studies is presented in Table 1. Some of the salient findings contained in Part 2 include the data showing that estrogen, specifically 17β-estradiol, can serve as an effective neuroprotectant. The other predominant female gonadal steroid hormone, progesterone, also can function as a neuroprotectant, but there is no indication that the male gonadal steroid hormone, testosterone, can function in this capacity. The antiestrogen, tamoxifen, appears to exert complex effects with evidence for and against neuroprotection. These conflicting findings may be related to the mixed agonist/antagonist actions of this nonsteroidal antiestrogen. Other estrogen-like agents illustrating neuroprotection include dehydroepiandrosterone and raloxifene. To be an effective neuroprotectant, the estrogen must be administered prior to treatment with a neurotoxin. These effects of estrogen can involve physiologic actions of this gonadal steroid and are present in at least three different neurotoxic agents. There appears to exist a critical developmental variable regarding estrogen's ability to function as a neuroprotectant, in that removal of estrogen prior to puberty abolishes the demonstration of a neuroprotective effect when tested in the adult. Finally, estrogen can function as a neuroprotectant in male mice treated with MPTP, but not methamphetamine; however, progesterone appears to act as a neuroprotectant against both neurotoxins in the male.

Part 3: Estrogen and NSDA Neuroprotection—Clinical Evidence

Introduction

Results from clinical studies assessing the effects of estrogen on the NSDA system can be quite complex, oftentimes yielding data that are difficult to interpret and seemingly contradictory. Some of the more notable methodological considerations contributing to this problem include continuous vs intermittent estrogen administration, dose of estrogen, age at administration, stage of disease, reproductive history (nulliparous, primiparous, or multiparous), medical history (hysterectomy, salpingo-oophorectomy), genetic susceptibility, and socioeconomic factors. Add to these issues the potentially important influence of a placebo effect in Parkinson disease (PD) and a further source of confound may be introduced to these experiments *(67)*. While remaining cognizant of these limitations, researchers have garnered a great amount of clinically significant data from these studies. In this part, we review some of the more salient data related to the relationship between estrogen and Parkinson disease and discuss the clinical arguments for symptomatic dopaminergic and neuroprotective effects of estrogen in Parkinson disease.

Menstrual Cycle and Parkinson Disease

In a manner analogous to the study of estrous cycle changes in NSDA function (see Gonadal Steroids and the NSDA System), the clinical influence of gonadal steroids on the NSDA system can be assessed across the menstrual cycle. Symptoms of Parkinson disease can fluctuate with the menstrual cycle, which is thought by most researchers to represent dopaminergic activity of estrogen. Estrogen levels show biphasic peaks, the first with ovulation and the second in the latter half of the cycle. Prior to menstruation,

Table 1
Synopsis of Data Providing Conditions/Variables
Under Which Gonadal Steroid Hormones Show Evidence
or No Evidence of Neuroprotection of the Nigrostriatal Dopaminergic System

Conditions/Variables	Evidence for Neuroprotection	No Evidence for for Neuroprotection
	1. Gonadal Steroids	
A. 17β-Estradiol	*40*[a]*,43,46–51,54*	
B. 17α-Estradiol		*52,53*
C. Progesterone	*52,55,58*	*55*
D. Testosterone		*51,56,59,60,64–66*
E. Dihydrotestosterone		*65*
	2. Estrogenlike Modulators	
A. Tamoxifen	*57*	*49*
B. 4-Hydroxytamoxifen	*55*	
C. Dehydroepiandrosterone	*59*	
D. Raloxifene	*52*	
	3. Temporal Factors	
A. Estrogen		
Neurotoxin	*54*	
0.5–24 h	*40,43,46–51,54,55,60*	
D–Wk		
B. Neurotoxin		
Estrogen		*54*
0.25–2 h		
1 wk		*49*
	4. Physiological Actions	
A. Estrous Cycle	*43*	
B. Serum Estradiol	*49*	
	5. Neurotoxins Tested	
A. MPTP	*40,46,47,52*	
B. Methamphetamine	*43,49–51,54,55,60*	
C. 6-OHDA	*48*	
	6. Developmental Effects	
A. Prepubertal Ovariectomy		*55,56*
	7. Estrogen in Males	
A. MPTP	*47,52*	
B. Methamphetamine		*51,55,60*
	8. Progesterone in Males	
A. MPTP	*52*	
B. Methamphetamine	*55*	

[a]Reference citations.

when levels are at nadir values, many women notice an increase in parkinsonism *(68)*. We observed a young woman with Parkinson disease in whom L-dopa hyperkinesia increased at the preovulatory period, with a maximum in the ovulatory phase when estrogen levels were highest. Premenstrually, when estrogen levels were low, hyperkinesia clearly diminished while parkinsonism increased *(69)*. These observations suggest chorea with high levels, and parkinsonism associated with low levels of estrogens, and, hence, a dopaminergic action of estrogens. However, there are data that question a dopaminergic effect of estrogen across the menstrual cycle. For example, it has also been reported in 10 prospectively studied menstruating women with Parkinson disease that the expected biphasic estrogen peaks during the cycle failed to show a significant correlation between the severity of Parkinson disease in the off-state and serum levels of estrogens. In these women, the severity of Parkinson disease fluctuated during the study period and most women had a history of premenstrual worsening of Parkinson disease *(70)*.

Gender Differences and Parkinson Disease

The salient gender differences in NSDA function reported in animal studies (see Gender Differences and the NSDA System) and, more significantly, the demonstration of gender differences in response to NSDA neurotoxins (see Gender Differences and NSDA Neuroprotection) raise the question: Do gender differences exist in the risk for Parkinson disease? In humans, there may exist some type of female resistance to parkinsonian neurodegeneration because many studies reveal a prevalence of men, although the results of epidemiologic observations are not equivocal and some studies do not find gender differences.

In 1993, Zhang and Roman *(71)* surveyed the influence of gender on Parkinson disease. Since many differences in risk factors, methodological aspects, medical facilities, and age distribution were present within the 27 regional populations that they included in their review, they minimized the influence of these variables by adjusting available data to a single standard population. Using this calculation, the average standardized ratios of female to male were 1:3.5 for prevalence studies and 1:3.4 for incidence studies. In 1996, Tanner and Goldman *(72)* reviewed the epidemiology of Parkinson disease and provided age-adjusted prevalences of 12 studies from Europe ($n = 5$), North America ($n = 3$), Japan ($n = 2$), and one each from China and Libya. The mean male-to-female ratio was 1.49 (ranging from 0.86 to 1.79, with an outlying value from China of 3.70—the mean ratio without China was 1.39). A very similar ratio, with men showing a higher total incidence rate *(13)* vs women (8.8; ratio of men to women: 1.47), was obtained as based on a study of 154 cases of Parkinson disease *(73)*. A slightly higher ratio was reported in a recent study from Spain that screened 1579 persons age ≥40 yr and detected 20 with Parkinson disease. The age-adjusted prevalence of Parkinson disease was greater in men (10.78) than in women (5.23; ratio of men to women: 2.06) *(74)*. Moreover, in a review of 34 Parkinson disease studies in which the gender of the patients was indicated, 28 (82%) had a greater proportion of males *(61)*. Note, however, that studies relying on medical records are probably more biased than population-based surveys.

Nevertheless, a number of more recent formal epidemiologic studies reveal a greater prevalence of Parkinson disease in males. In a cohort of 2863 individuals (65–84 yr of age) Baldereschi et al. *(75)* found 42 patients with Parkinson disease. The age-adjusted relative risk in men compared with women was 2.13 for Parkinson disease (PD) (95% confidence interval [CI]: 1.11–4.11). Interestingly, these male vs female ratios may even change over time. For example, when comparing the epidemiology of Parkinson disease in southwestern Finland in 1992 with 1971, a prevalence ratio for Parkinson disease in men vs women of 1.2 (not significant) in 1971 can be contrasted with 1.7 in 1992 ($p < 0.001$); the relative risk for Parkinson disease in men vs women was 0.9 (not significant) in 1971 and 1.9 ($p < 0.001$) in 1992 *(76)*. Because prevalence rates are affected by survival, Elbaz et al. *(77)* computed the remaining lifetime risk by combining the incidence rates of Parkinson disease with mortality rates for all causes in the population. The remaining lifetime risk of developing Parkinson disease was 2% for men and 1.3% for woman (ratio of men to women: 1.5). At least two hospital-based studies also indicated a greater number of men with Parkinson disease. In a case-control study with 377 consecutive Parkinson disease patients attending a movement disorders clinic, male gender was significantly associated with occurrence of Parkinson disease (odds ratio [OR]: 1.98; 95% CI: 1.34–2.92) *(78)*. Moreover**,** data from seven hospital-based record sources and from one population source generated a total sample of 1835 patients with a resultant men-to-women ratio of 1.5:1 *(79)*. An interesting functional demonstration of gender differences in Parkinson disease has been indicated from data of two reports showing that women with Parkinson disease are more likely to experience L-dopa-induced dyskinesia than men *(80,81)*.

It should be noted that a greater prevalence of Parkinson disease in males is not universally reported. In 1994, a French study of 3149 persons age >65 yr, found a prevalence ratio for Parkinson disease of 1.4%, without a significant difference between men and women *(82)*. Nor was there a gender difference from the data of a Dutch population–based door-to-door survey of 6969 persons age ≥55 yr. The prevalence of Parkinson disease from this study was 1.2% for men and 1.5% for women and prevalence increased with age: age-specific figures for men vs women were 0.4 vs 0.2% (55–64 yr), 1.2 vs 0.8% (65–74 yr), 2.7 vs 3.4% (75–84 yr), and 3.0 vs 4.8% (85–94 yr) *(83)*. Most notably, a joint analysis involving a very large sample comprising 18,506 subjects from seven community surveys in North and South Europe yielded no differences in prevalence of Parkinson disease between men (1.74%) and women (1.79%) *(84)*. Interestingly, the segregation ratios of persons at risk in all published families with autosomal dominant α-synuclein Parkinson disease do not differ significantly. In these families, with 426 persons at risk and 143 persons with overt Parkinson disease, the segregation ratio for men was 34.9% and for women, 31.9% ($p = 0.52$, χ^2 test), suggesting that men and women are equally at risk of acquiring α-synuclein Parkinson disease *(85)*. Finally, as based on a sample of 101 patients with autosomal recessive parkin-gene parkinsonism, an equal number of men ($n = 52$) and women ($n = 49$) patients were observed *(86)*.

It is clear that a plethora of variables contribute to these gender differences. Accordingly, a definitive statement regarding the existence or nonexistence of gender differences in Parkinson disease awaits future analyses in which these variables can be identified and controlled.

Effect of Estrogens on Extrapyramidal Disorders

The extensive laboratory evidence for a role of estrogen in modulating NSDA function (see Estrogen-Progesterone

and the NSDA System) evolved from data on estrous cycle modulation of the NSDA (see Gonadal Steroids and the NSDA System). In an analogous manner, do the menstrual cycle alterations in the symptomology of Parkinson disease suggest a role for estrogen in this process? Contraceptives and pregnancy can induce chorea, a hyperdopaminergic phenomenon. Note, however, that hormonal-induced chorea is only seldom seen in women, in spite of millions of pregnancies and contraceptive users. Therefore, some kind of susceptibility to estrogens must be present in these woman with chorea. Sydenham's chorea in childhood seems to confer a persistent hypersensitivity of dopaminergic activity *(31)*. However, the majority of reported patients with hormonal chorea did not have Sydenham's chorea, suggesting that other causes of dopaminergic hypersensitivity to estrogens are probably involved *(87–90)*. Some potential examples can include Moya-Moya disease *(91)*, antiphospholipid antibodies *(92)*, lupus erythematosus *(93,94)*, and Henoch-Schonlein purpura and congenital cyanotic heart disease *(31)*. We do not know whether patients with chorea resulting from contraceptive use are also predisposed to chorea gravidarum. The combination, however, is occasionally seen *(95)*.

Estrogen Therapy and Parkinson Disease

Several observations seem to favor a positive dopaminergic action of estrogens as a therapy for Parkinson disease. One early case report describes two patients taking L-dopa who experienced worsening of parkinsonism after discontinuation of estrogens *(96)*. A retrospective analysis among 10,145 elderly female nursing home residents with Parkinson disease, of whom 195 received estrogens, found estrogen users being more independent in activities of daily living, regardless of age and cognitive impairment *(97)*. In three placebo-controlled randomized double-blind trials, the effect of estrogens on motor function in Parkinson disease was analyzed. Premarin (0.625 mg daily vs placebo) administered during an 8-wk period to 20 postmenopausal women with Parkinson disease produced some beneficial effects. Mean on-time during waking hours significantly improved by 7% (9 h/wk of awake time; 95% CI: 5.73–14.9%) and mean off-time by 4% (4.4 h/wk of awake time; 95% CI: 1.54–7.16%) in estrogen-treated women; UPDRS part III scores (motor examination) improved 3.5 ± 3.4 points (95% CI: 1.02–5.18). There was no improvement in UPDRS part II scores (activities of daily living), a timed tapping score, and the Hamilton depression scale *(98)*. Positive effects of estrogens were also obtained in a crossover study in which eight postmenopausal women with fluctuating Parkinson disease were treated for 10 d with skin patches of estradiol or placebo. With this treatment, mean serum estradiol levels reached values as high as 24 times baseline. Estradiol significantly reduced the threshold dose necessary to provide antiparkinsonian efficacy with intravenously administered L-dopa from 29 ± 4 to 21 ± 4 mg ($p = 0.02$). The mean L-dopa dose necessary to induce dyskinesias appeared somewhat lower (23 ± 5 mg) during estradiol treatment than with placebo (29 ± 5 mg), but the difference was not statistically significant ($p = 0.17$). Mean on-time for placebo was 57 ± 2% of waking hours compared with 61 ± 4% with estradiol *(99)*. However, the third trial failed to show any beneficial effects of estrogens. In that trial, 12 postmenopausal woman with nonfluctuating Parkinson disease and L-dopa therapy took 2 mg of estradiol or placebo twice daily for 8 wk. Although this dose of estrogen is similar to the hormonal substitution therapy for postmenopausal complaints and postmenopausal osteoporosis, it produces lower serum levels than that observed in premenopausal women during the second half of their cycle. With this regimen, neither the UPDRS motor examination part nor subjective scores significantly improved with estrogen: UPDRS pretest, 10.57 ± 7.8 and posttest, 13.14 ± 9.1 *(100)*. Whether this lack of improvement was owing to the relatively low dose of estradiol remains a consideration in this report.

Clinical Evidence for Neuroprotection by Estrogens

Unlike that for laboratory research, a controlled experiment cannot be performed to assess the potential for estrogen to function as a neuroprotectant against Parkinson disease. Nonetheless, some very interesting and suggestive data have been collated on this topic. The reports that show a greater incidence of Parkinson disease in men (see Gender Differences and Parkinson Disease) provide an indication of a potential for neuroprotection by estrogen. Not only may there be a greater incidence, but the severity of Parkinson disease appears greater in men. This follows from a study based on 630 patients in which it was reported that women exhibit less severe parkinsonian motor features than men with the progression of Parkinson disease *(81)*. A retrospective hospital chart review study found that 34 postmenopausal woman with idiopathic Parkinson disease (duration less than 5 yr, not taking L-dopa or agonists) who took estrogens at some point in the past had a less severe UPDRS score (18.1 ± 10.8) than 104 without estrogens (27.0 ± 15.1), while estrogen use was negatively correlated with UPDRS score *(101)*. Related to these findings is a report that estrogen treatment in elderly female nursing home residents with Parkinson disease resulted in these users being more independent in activities of daily living *(97)*. In a population-based case-control study, it was reported that women with Parkinson disease had undergone hysterectomy (with or without unilateral oophorectomy) with a greater prevalence than control women (OR: 3.36; 95% CI: 1.05–10.77) *(102)*.

While the findings in these studies could be interpreted as neuroprotection by estrogens, a symptomatic effect cannot be ruled out. Other studies do not support the hypothesis of estrogen neuroprotection in Parkinson disease. In a population-based community survey comprising 167 women with Parkinson disease, postmenopausal estrogen use did not affect the risk of Parkinson disease *(103)*. Moreover, it

has been reported that the age of onset of Parkinson disease was lower by 5 yr in women who had used estrogens *(101)*.

Conclusion

The majority of studies in Parkinson disease suggest that estrogens exert dopaminergic activity, although the measured effects are only moderate. Remarkably, in clinical trials a dopaminergic effect is mainly shown in patients with fluctuating Parkinson disease. Therefore, it is possible that estrogens exert a dopaminergic effect mainly in patients with supersensitive DA receptors, which may be in accordance with the hypothesis of supersensitive DA receptors in hormonal chorea in women. As far as a neuroprotective action of estrogens is involved, there is indirect evidence from epidemiologic studies reporting that there are more men than women with Parkinson disease. This latter observation suggests a protective role of estrogens in women for the risk of Parkinson disease. However, the results of the epidemiologic observations are not unequivocal, and such findings cannot prove that a greater incidence in men is caused by the effects of estrogens. Unfortunately, there are no double-blind placebo-controlled long-term trials addressing estrogens and neuroprotection. However, there are clinical observations comparing women using estrogens with nonusers. A number of these studies also suggest a neuroprotective action of estrogens, although most of these studies do not rule out symptomatic effects of estrogens. If estrogen does exert a neuroprotective action in Parkinson disease, it must do so in the very early stages of this disease. There are data showing that nigral degeneration in Parkinson disease actually starts many years before the clinical symptoms emerge *(104)*, which leaves open the possibility that endogenous estrogens actually exert their neuroprotective action during the premenopausal presymptomatic years of Parkinson disease. At the moment, however, there are insufficient clinical arguments to apply estrogen replacement therapy in patients with Parkinson disease.

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