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REVIEW

Sex hormones and diseases of the nervous system

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The influence of gonadal hormones on neurological health and disease is a rapidly developing domain in fundamental and clinical neuroscience. Sex hormones, directly or via their neurosteroid metabolites, impact monoaminergic, cholinergic, and peptidergic neurotransmission and play essential roles in shaping brain organization and function under normal and pathological conditions. The clinical expression of various neurological disorders may be modified by hormonal fluctuations related to the menstrual cycle, pregnancy, menopause, and oral contraceptive use. Understanding these interactions could lead to targeted hormonal and antihormonal therapies for diverse neurological conditions, including but not limited to catamenial epilepsy, Parkinson disease, and acute intermittent porphyria.

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Introduction

This paper is dedicated with heartfelt gratitude to Dr. Seymour (Si) Reichlin whose mentorship during a fellowship in neuroendocrinology at Tufts (1987–1988) continues to inform my career. For neurologists such as myself, the scope of clinical neuroendocrinology broadens significantly when considering the pervasive influences of circulating gonadal hormones on neurological disease expression. This article examines the diverse range of central and peripheral nervous system disorders affected by reproductive hormone fluctuations. The review focuses predominantly on steroid–neural interactions in women, given that the relatively stable (tonic) pattern of androgen secretion in men makes it more challenging to delineate the roles of testicular hormones in the natural history of neurological disorders.

Hormonal changes associated with specific stages of the menstrual cycle, pregnancy, menopause, and exposure to exogenous sex hormones can impact the release and metabolism of neurotransmitters and neuromodulators, potentially triggering or altering the semiology of various neurological and neuropsychiatric conditions. This review covers the major categories of human neurological disease—vascular, metabolic, inflammatory, degenerative, and others—with emphasis on how these conditions manifest in women. Neurological disorders that respond to specific hormonal and antihormonal therapies are highlighted. The involvement of gonadal hormones in psychiatric conditions such as depression, psychosis, and premenstrual syndrome is covered in other sources (1).

Steroid–Neural Interactions

Sex steroids exert vital organizational and activational influences within the nervous system. Organizational effects entail the permanent differentiation of neural circuitry responsible for sexual dimorphism (masculinization or feminization) during critical periods of brain development. On the other hand, the activational effects of sex hormones in the mature brain are largely reversible, essential for regulating the hypothalamic-pituitary-gonadal axis (Figure 1) and establishing gender-appropriate patterns of sexual, aggressive, cognitive, and autonomic behaviors (1). The topographies of estrogen, progestin and androgen target neurons exhibit considerable overlap within the mammalian neuraxis (2, 3). In both sexes, estrogen-binding neurons are concentrated in the preoptic area, medial basal hypothalamus, medial amygdala, and circumventricular organs. Estrogen-binding neurons also reside, to a lesser extent, in the basal forebrain, hippocampus, several thalamic nuclei, sensory regions of the brainstem and spinal cord and the neonatal neocortex. In addition to neurons, some periventricular astrocytes also contain gonadal steroid receptors and undergo biochemical and morphological changes after chronic estrogen exposure (4, 5). The latter may account for the ability of sex steroids to modify patterns of growth and differentiation of certain human glial tumors.

In neurons, sex steroids and their metabolites regulate the biosynthesis of enzymes and structural proteins involved in neurotransmission, cell membrane function, energy metabolism, and hormonal sensitivity. At the molecular level, progestins, estrogens, and androgens interact with specific receptor proteins within the cytoplasm or nucleus of target cells. These steroid–receptor complexes can either activate or repress the transcription of various genes by binding to steroid response elements in their promoter regions. In addition to altering gene transcription profiles, sex steroids may influence neural functions through epigenetic regulation of cellular DNA methylation status (6). For example, estrogens influence the activity of DNA methyltransferases and reduce promoter methylation of brain-derived neurotrophic factor (BDNF), a protein critical for neuronal maturation and synaptic plasticity and implicated in Alzheimer disease (AD); testosterone impacts histone acetylation and methylation through modulation of histone acetyltransferases and histone deacetylases which may impact dopaminergic signaling in Parkinson disease (PD); and epigenetic modifications of the progesterone receptor may affect the natural history of breast cancer and endometriosis and their neurological complications (7–10). Sex hormones may also modulate neuronal discharges via rapid, nongenomic mechanisms. A significant pathway mediating the latter involves the central synthesis of neurosteroids from hormone precursors secreted by the ovaries, testes, and adrenal glands. Neurosteroids acutely modulate neuronal firing by altering GABA-A receptor–mediated chloride conductance, either enhancing or attenuating inhibitory signaling. Positive modulators like allopregnanolone, allotetrahydrodeoxycorticosterone, and androstanediol increase GABAergic transmission thereby reducing excitability, which may ameliorate epilepsy and mood disorders. Conversely, sulfated neurosteroids such as dehydroepiandrosterone sulfate and pregnanolone sulfate increase neuronal excitability by decreasing GABAergic tone and promoting calcium influx through NMDA receptors, neurophysiological effects which may support memory in AD and other dementing disorders (11–13).

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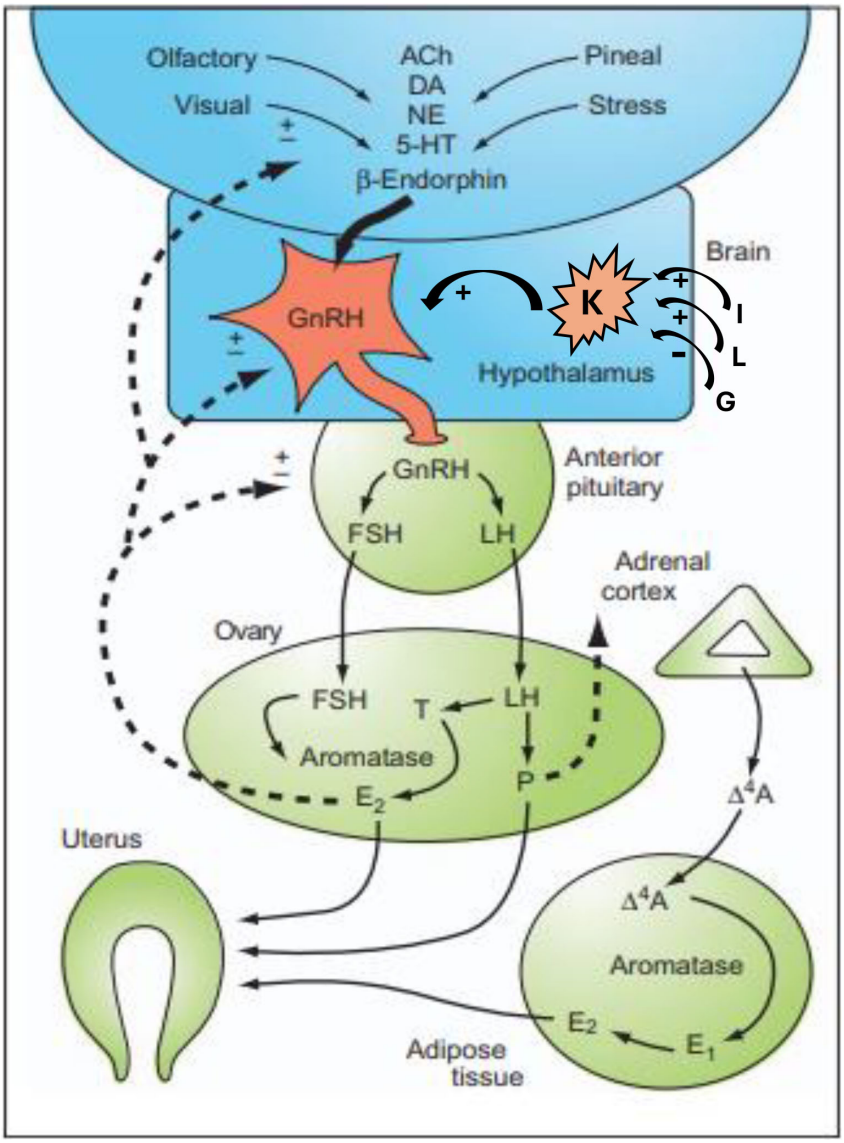

Figure 1. The brain-pituitary-ovarian axis (simplified). △4A, delta-4-androstenedione; ACh, acetylcholine; DA, dopamine; E1, estrone; E2, estradiol; FSH, follicle-stimulating hormone; G, ghrelin; GnRH, gonadotropin-releasing hormone; 5-HT, 5-hydroxytryptamine (serotonin); I, insulin; K, kisspeptin; L, leptin; LH, luteinizing hormone; NE, norepinephrine; P, progesterone; T, testosterone.

Migraine

Migraine, the most common type of vascular headache, is approximately three times more prevalent in adult women than men and may be over-represented in persons with endometriosis and the polycystic ovarian syndrome (14). Depending on the stringency of diagnostic criteria applied, anywhere from 18%–60% of female migraine sufferers experience a worsening of headaches around menstruation (catamenial migraine) (15). The intensity or frequency of migraine attacks often decreases during pregnancy, especially among those with menstrual-related migraines. However, many women who experience relief during pregnancy report a relapse of symptoms at or soon after childbirth. In some cases, breast-feeding may help prevent the recurrence of migraines. Migraine may also emerge or intensify during pregnancy or the perimenopausal phase (1).

The reduction in plasma estradiol (but not progesterone) during the late luteal phase is thought to play an important role in the onset of catamenial migraine. In pregnancy, the lack of cyclic estrogen withdrawal may help reduce migraine activity. Estrogens can affect migraine by acting directly on vascular smooth muscle or by modulating the activity of vasoactive substances at neurovascular junctions. Perimenstrual estrogen fluctuations may influence central serotonin, prostaglandin and/or opioid metabolism, which could stimulate vasoregulatory mechanisms in the hypothalamus or brainstem leading to symptomatic changes in cerebrovascular tone (16). Prolactin, which exhibits pronociceptive effects, and oxytocin, which has antinociceptive properties, have recently been implicated in the expression of migraine and may contribute to sex-dependent differences in the prevalence of this disorder (17). Prolactin directly sensitizes sensory neurons and increases the release of calcitonin gene-related peptide (CGRP), a neuromodulator that promotes migraine in susceptible patients and is currently a major therapeutic target (18). Additionally, the lower prevalence of migraine in adolescent and adult men relative to women of similar age may, in part, be androgen dependent in light of the antinociceptive effects of testosterone on sensory neurotransmission, CGRP release, neuroinflammation, and cerebrovascular tone (19).

Women using oral contraceptives may experience new-onset vascular headaches or an exacerbation of pre-existent migraine. These attacks typically occur during the initial cycles, especially on placebo days when estrogen levels drop, and generally subside once the contraceptive is discontinued. Migraine sufferers who develop focal auras while on oral

contraceptives may face a heightened risk of infarction in the affected brain areas (1).

Perimenstrual migraine is often manageable with dietary, psychological, and pharmacological approaches commonly used for migraine treatment in general. Sumatriptan and other serotonin 5-HT_{1D} receptor agonists are effective for both noncatamenial and menstrual migraines (20). For severe, refractory cases of catamenial migraine, late luteal phase therapy with prostaglandin inhibitors (nonsteroidal anti-inflammatory drugs) and/or mild diuretics may provide relief. Oral contraceptives may aggravate migraine and are probably best avoided in this context. Estrogen implants and the antiestrogen tamoxifen have shown mixed results. Some women have reported significant symptom relief from menstrual migraine following treatment with the testosterone derivative, danazol or the dopamine agonist, bromocriptine (16, 21). To avoid risks of teratogenesis, nonpharmacological methods (such as relaxation training and biofeedback) should be prioritized when managing migraine during pregnancy. Acetaminophen with codeine or nonsteroidal anti-inflammatory agents may be used for more severe episodes, while meperidine, morphine, chlorpromazine or glucocorticoids may be necessary for prolonged, refractory migraines (status migrainosus) during pregnancy. Hormone replacement therapy (HRT) may help with perimenopausal migraines, though this must be weighed against the potential risk of breast cancer. For women experiencing perimenopausal migraine with hot flashes, venlafaxine or fluoxetine may be of benefit (1).

In addition to migraine, factors such as menstruation, pregnancy, and menopause may impact the presentation of cluster headaches, paroxysmal hemicranias, and other trigeminal autonomic cephalalgias (22).

Stroke

The use of oral contraceptives has been identified as a significant risk factor for thromboembolic cerebral infarction, cerebral venous thrombosis, and subarachnoid hemorrhage. Risk factors such as age over 35, hypertension, smoking, and migraine further increase stroke risk for individuals on oral contraceptives. Recent declines in thromboembolic disease rates among oral contraceptive users are likely due to reduced doses of estrogen in modern formulations (e.g., 25–35 μg compared to earlier 50–75 μg preparations). Ultra-low-dose oral contraceptives ($<$25 μg ethinyl estradiol) may not elevate stroke risk in normotensive, nonsmoking individuals (23). There is, however, conflicting evidence regarding HRT and its effects on stroke incidence, with some studies showing neutral, increased, or decreased risk. Notably, large, randomized trials have demonstrated that HRT with 17β-estradiol or conjugated equine estrogen, with or without medroxyprogesterone acetate, may worsen outcomes for women predisposed to stroke or coronary artery disease (24, 25). Conversely, HRT with transdermal low-dose estrogens, alone or combined with micronized progesterone, may be beneficial in minimizing chances of ischemic stroke (1). Men with the common ESR1 c.454-397CC variant of the estrogen receptor-α (ERα) gene may be more vulnerable to ischemic stroke than those with other ERα genotypes, after adjusting for age, smoking, diabetes, hypertension, and lipid levels (26). The pathophysiology of sex steroid–related stroke, in particular the multifaceted impact of gonadal hormones on circulating lipid profiles, coagulation factors, platelet function, and atherogenesis, is reviewed elsewhere (1, 27).

Clinically, ischemic strokes linked to oral contraceptive use are localized to both the carotid (primarily the middle cerebral artery) and vertebrobasilar systems. In young women with oral contraceptive-related stroke, neuroimaging or pathological evidence of widespread vascular disease is typically absent (28).

Exogenous gonadal hormones should be promptly discontinued and may be unsuitable for future use in young women who present with a stroke syndrome. Management of ischemic stroke related to hormone exposure should follow general protocols, including standard pharmacotherapy (antiplatelet agents, anticoagulants, fibrinolytics), interventional neuroradiology (e.g., mechanical thrombectomy, stents) and rehabilitation. Early implementation of intravenous thrombolysis (tissue plasminogen activators) may benefit both men and women with acute ischemic stroke, though re-canalization (reperfusion) tends to be more effective in women (3, 29).

Former and current users of moderate- to high-dose oral contraceptives have an estimated fourfold increased risk of subarachnoid hemorrhage compared to the general population. However, the odds ratio for hemorrhagic stroke in current users of low-dose estrogen contraceptives (20 to 35 μg) is negligible relative to former users or nonusers. Similar to ischemic stroke, factors such as cigarette smoking and age over 35 significantly increase the occurrence of subarachnoid hemorrhage in oral contraceptive users (1). Gender differences in intracerebral hemorrhage due to hypertensive arteriopathy, amyloid angiopathy, vascular malformations, and Moyamoya disease have also been documented (1, 30). In rare cases of periodic subarachnoid hemorrhage due to spinal canal endometriosis, treatment may include progestins, GnRH agonists/antagonists, oophorectomy, and possibly vascular endothelial growth factor receptor inhibitors (e.g., sunitinib) (3, 31).

Movement Disorders

Parkinson Disease

Idiopathic PD is an aging-related movement disorder characterized by degeneration of dopaminergic neurons in the substantia nigra that occurs about twice as frequently in men than women. Interestingly, female predominance has not been observed in leucine-rich repeat kinase 2 (LRRK2)-associated PD, the most common monogenic form of the illness (32). A large-scale study comparing drug-naïve men and women with early-stage idiopathic PD, matched for motor impairment, found notable gender differences in nonmotor symptoms: men showed more pronounced deficits in olfaction and in specific cognitive areas (global cognition, memory, and visuospatial skills), while women exhibited higher levels of trait anxiety (32, 33). Initial anecdotal reports indicated that exposure to exogenous estrogen may worsen both idiopathic and neuroleptic-induced parkinsonism, ostensibly by dampening dopaminergic neurotransmission in the nigrostriatum. However, studies on premenopausal women with idiopathic PD disclosed perimenstrual worsening of motor symptoms when estrogen levels decline (1, 34). The effects of postmenopausal HRT in women with PD are mixed, with reports suggesting HRT may be beneficial (35–37), detrimental (38) or inconsequential (39). Early menopause, whether natural or surgical, has been identified as a possible risk factor for PD (40, 41), which may be mitigated by postmenopausal estrogen replacement (41). However, a large prospective study found no evidence that estrogen reduces the risk of developing PD. Additionally, a case-control study identified steroid contraception as a potential PD susceptibility factor, with an adjusted odds ratio of 3.27 [95% confidence interval (CI): 1.24–8.59; $p = 0.01$] (42). Sex differences in responses to treatment of PD have been recognized and may be driven, at least in part, by hormonal factors. Men tend to respond better to motor symptom control with dopaminergic agents and deep brain stimulation (DBS) than women; the latter may be more prone to levodopa-induced dyskinesias (involuntary movements) and are more likely to experience mood-related adverse effects of DBS (32, 43).

Of potential therapeutic interest, cerebrospinal fluid and plasma levels of allopregnanolone are reportedly low in idiopathic PD. This neurosteroid has been shown to stimulate neurogenesis in the substantia nigra, modulate dopamine release and enhance motor control in animal models of the disease (3, 44).

Wilson Disease

Wilson disease is a rare genetic disorder of copper metabolism marked by low blood ceruloplasmin levels, hepatic cirrhosis, copper deposits in the cornea (Kayser–Fleischer rings) and degenerative changes in the basal ganglia. In both healthy individuals and patients with Wilson disease, serum ceruloplasmin and copper levels may rise during pregnancy and following the use of steroid contraceptives. In women with Wilson disease, diagnosis may be delayed due to the "normalization" of ceruloplasmin levels following steroid contraceptive use. This false normalization provides no therapeutic benefit and may even be linked to neurological decline (e.g., abnormal movements, seizures, psychosis) in some cases (1, 45). It is unknown whether gonadal hormones similarly elevate ceruloplasmin levels in other conditions featuring abnormally low concentrations of the protein, such as acquired copper deficiency and hereditary aceruloplasminemia (46).

Chorea

Choreiform movements (jerky, nonrhythmic motions involving the face and extremities) may arise as complications of pregnancy (chorea gravidarum) and oral contraceptive use. Chorea associated with pregnancy and oral contraceptives is more common in individuals with a history of rheumatic fever or Sydenham's chorea. Oral contraceptives may also induce chorea in women with a background of congenital cyanotic heart disease, the antiphospholipid antibody syndrome, systemic lupus erythematosus and Henoch-Schönlein purpura; and they may exacerbate dyskinesias in chorea-acanthocytosis (1). Approximately 20% of affected women may experience relapses during future pregnancies. Women with dyskinesias linked to oral contraceptive use are at increased risk of developing chorea gravidarum and the reverse is true as well (1). Hormonal changes associated with pregnancy and the use of steroid contraceptives can unmask latent chorea by enhancing dopaminergic neurotransmission in basal ganglia previously damaged by hypoxic or rheumatic encephalopathy (1, 47).

Women with gestational or contraceptive-related chorea may also experience fever, neuropsychiatric symptoms, dysarthria (slurred speech), pendular reflexes or limb hypotonia. Chorea gravidarum and dyskinesias related to contraceptive use generally resolve following childbirth or upon discontinuation of the medication. In cases of suspected chorea gravidarum, clinical and laboratory assessments are recommended to rule out other causes, such as hyperthyroidism, rheumatic fever, Wilson disease or systemic lupus erythematosus. Since chorea gravidarum is typically self-limiting, abortion or early delivery is seldom necessary. In more severe cases, dopamine antagonists (neuroleptics) may provide symptom relief. Those with a history of chorea gravidarum or contraceptive-induced dyskinesias should likely avoid further use of estrogen-containing medications (1, 47).

Other Movement Disorders

Variations in gonadal hormone levels and/or sex steroid–related symptom fluctuations have been reported in patients with tardive dyskinesia, Tourette syndrome, hemiballismus, restless legs syndrome, hereditary and posthypoxic myoclonus, familial episodic ataxia, dominantly inherited myoclonic dystonia, the neuroleptic malignant syndrome, drop attacks, progressive supranuclear palsy and the Woodhouse–Sakati syndrome (1, 48).

Epilepsy

The course of epilepsy and its management can be significantly affected by various phases of the reproductive cycle and exposure to hormonal contraceptives. Certain seizure disorders may worsen premenstrually (catamenial epilepsy), at ovulation or during pregnancy. A large study (49) found that menstrual irregularity between ages 18 and 22 was associated with a higher risk of epilepsy (relative risk 1.67, 95% CI: 1.12–2.51). Although the menstrual cycle and oral contraceptives appear to have limited clinical effects on anticonvulsant pharmacokinetics, gestational plasma levels of phenobarbital, phenytoin and valproic acid may drop by 30%–40% from pre-pregnancy levels, with smaller decreases seen for carbamazepine. Primidone levels generally remain stable, though the concentration of its metabolite, phenobarbital may be reduced during pregnancy (1).

Seizure disorders and their treatments can interfere with normal reproductive functions (50). Conditions such as hypogonadotropic hypogonadism, polycystic ovary syndrome, and hyposexuality may result from abnormal limbic discharges in patients with temporal lobe epilepsy (1). Curiously, left-sided temporal lobe seizures are more likely to cluster at the onset of menses, whereas right-sided temporal seizures tend to occur more randomly throughout the menstrual cycle (50).

Estrogens and progestins exhibit opposing effects on seizure activity, with estrogens being epileptogenic and progestins having anticonvulsant properties (50). Estrogens and certain sulfated neurosteroids enhance glutamatergic neurotransmission while reducing GABAergic activity, thereby promoting epileptogenesis, whereas progesterone and specific pregnane and androstane neurosteroids counteract these effects. Perimenstrual seizure activity may be triggered by an increased estrogen-to-progesterone ratio during the late luteal phase. Similarly, elevated estrogen-to-progesterone ratios typical of polycystic ovary syndrome may partly explain the frequent association of this infertility condition with temporal lobe epilepsy. Estrogen-progestin contraceptives do not appear to significantly worsen seizure control in women with epilepsy (1) and the impact of HRT on seizure control in epileptic postmenopausal women is minimal or nil (51). However, elevated estrogen levels resulting from gonadotropin therapy for assisted reproduction may worsen seizures in epileptic women; and interactions between enzyme-inducing anticonvulsants and hormones used in gender-affirming treatment for transgender individuals are also of concern (1). In gestational epilepsy, factors such as insufficient anticonvulsant levels, sleep deprivation and stress are often more critical determinants of seizure activity than direct hormonal triggers. Decreased drug compliance, lower bioavailability, increased distribution volume and enhanced metabolic clearance contribute to reduced anticonvulsant levels during pregnancy (1, 51).

Oral contraceptive failure is more common in women with epilepsy who are treated with phenobarbital, primidone, phenytoin, carbamazepine, and ethosuximide (52). Topiramate and felbamate may also affect gonadal hormone pharmacokinetics, reducing contraceptive effectiveness (53). While valproic acid does not reduce contraceptive efficacy, it may induce hyperandrogenism and the polycystic ovary syndrome. Oral contraceptive failure is generally not an issue for women taking vigabatrin, gabapentin, levetiracetam, clobazam, zonisamide, lacosamide, or lamotrigine (1). Tiagabine may cause breakthrough bleeding, though its overall effect on gonadal steroid metabolism is small (54). Most anticonvulsants associated with oral contraceptive failure induce the hepatic cytochrome P450 enzyme system (e.g., CYP3A4), thereby accelerating the breakdown of reproductive steroids. Additionally, anticonvulsants can (a) increase the production of sex hormone-binding globulins, leading to lower levels of circulating free (active) hormones, and (b) enhance the clearance of gonadal hormones by promoting their sulfate conjugation and glucuronidation in the liver and intestines (1).

Management strategies for catamenial epilepsy include: (1) premenstrual or periovulatory increases in anticonvulsant doses or the addition of an adjunct antiepileptic drug, such as clobazam; (2) cyclic use of a mild diuretic, like acetazolamide, which has modest anticonvulsant properties; and (3) progesterone supplementation, administered orally or via suppository (55, 56). During pregnancy, more frequent monitoring of antiepileptic drug levels is advisable, with dose adjustments (typically increases) as needed. Early-phase clinical trials have evaluated the antiepileptic properties of ganaxolone, an analog of allopregnanolone (3α-hydroxy-3β-methyl-5α-pregnane-20-one), which acts as a positive allosteric modulator of GABA-A receptors. Ganaxolone has shown promise in animal models and, in randomized, placebo-controlled trials, reduced seizure activity in adults with drug-resistant partial-onset seizures and children with refractory infantile spasms. The drug was generally safe and well tolerated, with dizziness and fatigue being the most commonly reported side effects (57, 58). Ganaxolone lacks hormonal activity thereby precluding potential risks associated with progestin therapy (59).

Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the central nervous system (CNS), most commonly diagnosed in men and women during their reproductive years. An earlier age at puberty may be a predisposing factor for MS in girls but not boys (60). While oral contraceptive use does not appear to impact the risk of developing MS, it may delay the disease's onset (61). Contrary to previous medical assumptions, the overall effect of pregnancy on MS-related morbidity is minimal (62). While MS symptoms may worsen in the first 3 months postpartum, this is often balanced by an improvement in disease activity during the third trimester (63). The reduction in disease burden during the third trimester in MS (and other immune-mediated conditions) is likely due to a state of relative maternal immunosuppression, which helps prevent rejection of the semiallogenic fetus. A host of circulating steroidal and protein factors has been implicated in pregnancy-related immunosuppression including α-fetoprotein, cortisol, estradiol, human chorionic gonadotropin (hCG), human placental lactogen, interleukin-10, pregnancy-associated glycoprotein, progesterone, 1,25-dihydroxyvitamin D_3, and allopregnanolone

(1, 64, 65). The influence of menopause on the natural history of MS is uncertain (66).

MS attacks during pregnancy can be managed with intravenous steroids. Interferons should be discontinued at least three months before planned conception and are not recommended during pregnancy or breastfeeding. An Israeli study reported that none of 14 pregnant women with relapsing-remitting MS who received prophylactic intravenous immunoglobulins immediately after delivery experienced a relapse within the following 6 months (67). Preliminary findings suggested that oral estriol may be beneficial for women with MS, and transdermal testosterone may offer benefits for men with the condition (68). A recent literature review concluded that estriol may have modest anti-inflammatory, and possibly neuroprotective, effects when administered as an adjunct to first-line immunomodulatory medications in female patients with MS (69). Women, especially during their reproductive years, tend to exhibit more robust responses than men to first-line disease modifying treatments such as interferon-beta and glatiramer acetate. However, women may experience more pronounced untoward effects (liver enzyme elevation, lymphopenia) of fingolimod and dimethyl fumarate, and may be at higher risk than men for infusion-related reactions and autoimmune complications accruing from monoclonal antibody (natalizumab, ocrelizumab) exposure (70, 71).

Commonly used immunomodulatory medications for the management of MS, such as beta-interferon, glatiramer acetate, dimethyl fumarate and fingolimod, do not appear to diminish the effectiveness of hormonal contraception. Less is known regarding the potential impact of natalizumab, ocrelizumab, ofatumumab and other anti-MS biologics on sex steroid metabolism (72).

Alzheimer Disease

AD is a prevalent form of dementia marked by progressive neuronal degeneration, gliosis, significant depletion of acetylcholine and other neurotransmitter imbalances and the buildup of amyloid plaques and neurofibrillary tangles in the basal forebrain, hippocampus, and association cortex (73). By the turn of the millennium, promising reports suggested that estrogens play an important role in normal human cognition, have beneficial effects on Alzheimer symptoms and protect normal women and those with Down syndrome against the development of AD (1, 74). Evidence was also adduced suggesting that postmenopausal estrogen replacement therapy may stave off dementia in women with PD (75) and that testosterone (76, 77) or estrogen (78) treatment may confer cognitive benefits to elderly men with AD or mild cognitive impairment. Fundamental research had shown that estrogens exert trophic effects on cholinergic neurons in the rodent basal forebrain, promote dendritic spine (synapse) formation, activate functional N-methyl-D-aspartate receptors (important for memory) in the adult rat hippocampus and induce significant neuritic growth in rodent hypothalamic explants. Estrogens also exhibit antioxidant properties, reduce the deposition of fibrillar β-amyloid, modulate apolipoprotein E expression, suppress inflammatory responses associated with neuritic plaque formation and increase cerebral blood flow and glucose utilization—both of which are deficient in individuals with AD (1). More recently, sex steroids have been implicated in AD pathophysiology via their effects on autophagy, epigenetics, glymphatic function and the gut microbiome (79–81). Other reproductive hormones, such as prolactin, oxytocin, and follicle-stimulating hormone, and several X-chromosome coded genes (e.g., the demethylase gene, *kdm6a*), may also contribute to sex-specific manifestations of AD pathology (82).

Despite the initial optimism, in the randomized Heart and Estrogen/Progestin Replacement Study (HERS), cognitive function scores showed no difference between women treated with estrogen and progestin and those receiving a placebo (83). Furthermore, in the large Women's Health Initiative Memory Study (WHIMS), the hazard ratios for developing dementia were 1.49 for women randomized to receive 0.625 mg of conjugated equine estrogen and 2.05 for those receiving 0.625 mg of estrogen plus 2.5 mg of medroxyprogesterone acetate, compared to placebo-treated controls (84)! Based on these disappointing findings, current guidelines advise against using estrogen/progestin replacement therapy to reduce dementia risk in postmenopausal women. Nor is there sufficient evidence to support or oppose the prescription of androgen replacement for cognitive dysfunction in elderly men (1). Some have argued that the large therapeutic trials may have overlooked a critical perimenopausal "window" during which HRT might help protect against AD. Further confounding interpretation, hot flashes have been associated with greater brain amyloid burden. It is therefore is possible that women experiencing severe menopausal symptoms—and who are more likely to use estrogen replacement therapy—may be at increased risk of dementia that is independent of hormonal exposure (85). Recent, large meta-analyses may permit more nuanced insight into the role(s) of HRT as a modifier of dementia risk: Data from 34 randomized controlled trials involving 14,914 treated participants and 12,679 controls indicated that estrogen-only therapy initiated during midlife or close to menopause onset was associated with improved verbal memory. In contrast, estrogen-progestogen therapy administered in late life was linked to declines in several cognitive domains (86). In apolipoprotein E4 (APOE4) carriers enrolled in the European Prevention of Alzheimer's Disease (EPAD) Cohort, HRT was associated with larger entorhinal and amygdala volumes and improved delayed memory, suggesting a targeted strategy to mitigate AD in this high-risk subpopulation (87).

Neurosteroidogenesis may play a role in the pathophysiology of AD (88). Studies have reported reduced levels of DHEA-S in plasma and cerebrospinal fluid, as well as lower allopregnanolone concentrations in the prefrontal cortex, of individuals with this condition. Allopregnanolone may support cognitive health by reducing β-amyloid pathology, suppressing microglial activation (neuroinflammation), enhancing hippocampal neurogenesis and reversing learning and memory deficits in animal models of AD (1). It remains to be determined whether modulation of central neurosteroid biochemistry can be leveraged to therapeutic advantage in patients with AD and other dementing afflictions.

Sleep Disorders

In women, sleep architecture is influenced by puberty, menstruation, pregnancy, and menopause. Sleep-related complaints are generally more common in women than men. Gender differences in sleep patterns emerge after puberty and may increase susceptibility to sleep disorders. For instance, insomnia is more prevalent in women, with the gender gap widening as age advances. Restless legs syndrome also occurs more often in women, while obstructive sleep apnea and rapid eye movement (REM) sleep behavior disorder are more frequent in men (89, 90).

The mechanisms by which altered gonadal hormone levels and their effects on neural targets within the diencephalon and brainstem influence human sleep physiology remain poorly understood. In women, hypogonadism may disrupt normal sleep architecture by prolonging sleep latency, reducing REM sleep periods and increasing nocturnal movement arousals (91). In addition to the effects of fluctuating gonadal steroid concentrations, follicle-stimulating hormone may contribute to disruption of sleep patterns during the menopausal transition (92). Hyperandrogenism complicating the polycystic ovarian syndrome may predispose to obstructive sleep apnea in women (*ibid*.). The higher prevalence of obstructive sleep apnea in men may be attributed not only to differences in gonadal steroid profiles but also to sex-based variations in neuromuscular reflexes and central ventilatory control (89). Complex interactions between sex hormones and melatonin, a neurohormone secreted by the pineal gland, may impact sleep behavior in men and women. Estrogen and melatonin mutually affect each other's metabolism and jointly regulate sleep-wake cycles and REM sleep patterns; progesterone enhances melatonin synthesis which, in turn, may promote restorative sleep in persons with sleep apnea; and testosterone may suppress melatonin secretion and thereby contribute to sleep disturbances in aging men (93–96).

In a study of 33 postmenopausal women, combined estrogen-progesterone therapy reduced breathing irregularities, periodic limb movements, nocturnal arousals, hot flashes, and bruxism (teeth grinding) (97). For patients with central sleep apnea, progestins may help reduce hypoventilation by stimulating brainstem respiratory centers. However, administration of progesterone to healthy men may decrease wakefulness and vigilance, effects potentially mediated by the GABAergic

agonists, pregnanolone and allopregnanolone (98). It is noteworthy that certain medications used to treat narcolepsy—modafinil, armodafinil, and pitolisant (but not solriamfetol)—induce CYP3A4 and may thereby cause hormonal contraceptive failure (99).

Nervous System Neoplasms

Meningiomas

Meningeal tumors are more common in women than in men during reproductive age and are ostensibly more frequent in women who are obese or have hormone-dependent breast cancer (1). A large Finnish study reported an increased incidence of meningiomas in women undergoing HRT (100). A substantial proportion of human meningioma specimens express progestin-binding proteins, and to a lesser extent, estrogen- and androgen-binding proteins (101). Elevated circulating estrogen levels, accruing from the conversion of androstenedione to estrone in adipose tissue, may account for the higher prevalence of meningiomas in obese individuals (1).

Women may experience exacerbation of meningioma-related symptoms during the luteal phase of the menstrual cycle. Clinical and radiological evidence also indicates rapid growth of meningiomas during pregnancy, often followed by spontaneous regression postpartum (102). Meningiomas that lack progesterone receptors tend to show higher mitotic indices, increased necrosis, greater likelihood of brain invasiveness and shorter disease-free intervals (103, 104). The antiprogestin agent mifepristone (RU 486) has been reported to stabilize or reduce the growth of meningiomas *in situ*. However, the effects of progestins and mifepristone on meningioma growth *in vitro* are contradictory (105). A placebo-controlled, phase-3 trial of mifepristone involving 164 women with meningioma was considered underpowered and therefore inconclusive (106). As a cautionary note, patients undergoing chronic RU 486 treatment may require glucocorticoid replacement to offset the drug's antiglucocorticoid effects (107). Concerns have also been voiced that gender-affirming treatment with estrogens, progestogens or cyproterone acetate (a progestin with antiandrogen properties) may stimulate meningioma growth in transgender women (1).

Other Tumors

Astrocytomas can selectively bind estrogens, progestins, or androgens. In astroglial tumors, estrogen receptor-β expression often correlates inversely with the degree of histopathological dedifferentiation and malignancy (108). Astrocytomas have been observed to expand during pregnancy and regress in the postpartum period. Some patients with astrocytomas or glioblastoma multiforme have shown clinical and radiological stability following treatment with the antiestrogen tamoxifen (3). In this context, the radiosensitizing properties of tamoxifen or its inhibitory effects on protein kinase C activity may play a more significant role than its antiestrogenic actions (1). Gonadal steroid receptors and/or responsiveness to reproductive hormones have also been identified in oligodendrogliomas, pituitary adenomas, acoustic neuromas, anaplastic ependymomas, hemangioblastomas, primitive neuroectodermal tumors, lymphomas, and breast cancer metastases to the CNS (3). Direct prostate cancer metastases to the CNS are rare and their sensitivity to androgen deprivation therapy is not well documented (109, 110).

Intracranial Hypertension

Estrogen-related attenuation of the blood-brain barrier may contribute to the pathogenesis of idiopathic intracranial hypertension (pseudotumor cerebri) in humans, potentially explaining the strong female predisposition to this disorder. Estrogens increase cerebral endothelial cell permeability and post-traumatic brain edema in female rats. Progesterone, on the other hand, reduces posttraumatic cerebral edema and intracranial hypertension in rodents, an effect attributed to decreased blood-brain barrier permeability and inhibition of cerebrospinal fluid production by the choroid plexus. Gonadal steroids may impact the pathophysiology of idiopathic intracranial hypertension by their effects on the brain's glymphatic system. The latter comprises a recently recognized network of perivascular spaces that enables the movement of interstitial fluid, solutes and waste products between the cerebral vasculature and the cerebrospinal fluid (111).

Idiopathic intracranial hypertension may be more prevalent in women with polycystic ovary syndrome and hyperandrogenism, as well as in female-to-male transgender individuals receiving intramuscular testosterone (112). Data on the risk of pseudotumor cerebri in women using hormonal contraception are inconclusive (113).

Neuromuscular Disorders

Myasthenia Gravis

Myasthenia gravis is an autoimmune, neuromuscular disorder characterized by fatigable weakness of striated (voluntary) muscle. Estrogens may contribute to the female preponderance of myasthenia gravis and other autoimmune disorders of the neuromuscular junction by facilitating the maturation of Th2 cells, antibody-producing B cells, and thymic epithelial cells. Thymocytes of female myasthenic patients overexpress estrogen receptor α subunit (ER-α) which may be responsible, at least partly, for the relatively high prevalence of thymic hyperplasia in this population. Estrogens may also augment female vulnerability to myasthenia by epigenetically silencing the autoimmune regulator (AIRE) gene. Conversely, dihydrotestosterone enhances thymic tolerance and dampens autoimmunity by upregulating AIRE expression through its interaction with the androgen response element in the AIRE promoter (114).

The Porphyrias

The porphyrias are characterized by an increased production of porphyrin precursors and porphyrins due to enzymatic defects in heme biosynthesis. Common neurological manifestations of certain porphyrias include sensorimotor and autonomic neuropathies, neuropsychiatric symptoms and seizures. Estradiol and other steroid hormones can precipitate porphyric crises by stimulating the heme biosynthetic enzyme, δ-aminolevulinic acid synthase. In women with acute intermittent porphyria, episodes of neuropathy and other neurological symptoms may arise during the late luteal phase, at ovulation or during pregnancy (115).

Long-term administration of GnRH agonists, such as leuprolide or D-His, downregulates GnRH receptors in the pituitary leading to sustained suppression of the pituitary-ovarian axis. An early study reported complete remission of catamenial acute intermittent porphyria during an 8-month course of D-His treatment (116). Subsequent cases of perimenstrual acute intermittent porphyria (117) and hereditary coproporphyria (118) also showed positive responses to GnRH agonist therapy. However, prolonged use of GnRH analogs or antagonists may result in adverse effects such as breast tissue atrophy, hot flashes, and bone demineralization (*ibid*.). It is advisable that asymptomatic relatives of patients with genetic porphyrias avoid exposure to oral contraceptives.

Endometriotic Sciatica

Ectopic endometrial tissue (endometriosis) responds to steroid hormones and undergoes sloughing and bleeding during menstruation. Endometriosis can lead to back or pelvic pain by invading the lumbar vertebrae, lumbosacral plexus or sciatic nerve sheath. This can result in radicular pain, typically beginning a few days before menstruation and persisting until the end of the cycle (catamenial sciatica). Symptoms such as leg weakness, numbness, and loss of ankle reflexes may accompany the pain. Unlike discogenic radiculopathy, neuroimaging in cases of endometriotic sciatica often appears normal and signs of endometriosis in other areas may or may not be evident. Surgical exploration of the sciatic nerve may be necessary for diagnosis. In confirmed cases, the nerve appears blue and incision of the sheath releases a dark, hemorrhagic fluid. Histopathological examination reveals characteristic glandular structures (28, 119).

Symptoms of endometriotic sciatica are generally less responsive to bed rest compared to far more common discogenic radiculopathy. However, the former may show significant improvement with standard endometriosis treatments, including progestins, GnRH agonists, and antagonists (e.g., leuprolide and elagolix, respectively), or, in refractory cases, oophorectomy (28, 120).

Other Neuromuscular Disorders

Endogenous and administered gonadal steroids, primarily estrogens, may influence the progression of carpal tunnel syndrome, Bell's palsy and recurrent brachial plexopathy. These effects may largely be due to hormone-related soft tissue swelling leading to nerve compression. In

men with myotonic dystrophy, dysfunction of testicular peritubular myoid cells may contribute to hypergonadotropic hypogonadism and impotence (121). Hyperestrogenemia has been observed in male patients with Duchenne muscular dystrophy, amyotrophic lateral sclerosis, bulbospinal muscular atrophy (Kennedy syndrome), POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes linked to plasma cell dyscrasias) and Kugelberg–Welander disease (1). The role, if any, of hyperestrogenemia in the pathogenesis of these neuromuscular disorders remains unclear. High-dose testosterone has been reported to alleviate symptoms in a patient with bulbospinal muscular atrophy, potentially by attenuating the toxic gain of function linked to the mutated androgen receptor in this condition (122).

Conclusions

One fine morning on Rounds some 36 years ago, Si quipped that "neuroendocrinology is a discipline in search of a disease" [pers. commun.]. While it is indisputable that diseases of the neuroendocrine hypothalamus are rare entities relative to, say, diabetes mellitus, dyslipidemia, and primary thyroid conditions, the scope and volume of clinical material expand dramatically when the purview of clinical neuroendocrinology is understood to encompass the myriad influences of gonadal hormones on the expression of diverse neurological disorders. Sex steroids exert powerful organizational and activational effects within the mammalian nervous system, affecting a broad range of normal and pathological neurological functions. Estrogens, progestins, and androgens may modulate the activity of salient neural pathways directly via classical transcriptional, epigenetic and neurophysiological mechanisms, or serve as precursors of bioactive neurosteroids.

Links between reproductive hormones and the manifestations of migraine, stroke, epilepsy, chorea, and porphyria have been amply documented. In conditions such as PD, sleep apnea, CNS neoplasms and MS, robust sex hormone influences appear likely in light of accumulating epidemiological, clinical, and neuroimaging evidence. Fluctuations in sex hormone levels can also impact psychiatric states, including late luteal phase dysphoria (premenstrual syndrome), major depressive disorder, psychosis, and anorexia nervosa (1). Given the pervasiveness of steroid–neural interactions, clinicians should routinely query symptom variability related to the menstrual cycle, pregnancy, menopause and hormonal contraceptive use in women with neurological and psychiatric illnesses. Further exploration of the molecular mechanisms underlying both the salutary and adverse effects of sex steroids on neurological health may guide the development of new hormonal and antihormonal therapies for many of the conditions discussed in this review.

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After completing his residency training in neurology at Columbia University, Dr. Schipper did a fellowship in neuroendocrinology at Tufts University under the tutelage of Dr. Seymour Reichlin (1987–1988). In the clinic, he participated in the management of patients with a wide range of hypothalamic-pituitary disorders. In Dr. Reichlin's laboratory, Dr. Schipper extended his doctoral thesis work (1976–1982) on the pathological effects of estradiol on the hypothalamic arcuate nucleus in a rodent model of polycystic ovary syndrome.

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