The Impact of Gonadal Hormones on the Expression of Human Neurological Disorders

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Key Words

Alzheimer disease · Epilepsy · Estrogen · Menopause · Menses · Movement disorder · Multiple sclerosis · Neoplasm · Oral contraceptive

Abstract

The effects of gonadal steroids on neurological well-being and disease constitute a rich and rapidly expanding area of basic and clinical neuroscience. Gonadal hormones exert potent effects on monoaminergic, cholinergic and peptidergic pathways as well as neurosteroidogenesis which, in turn, impact normal brain organization and function. A spectrum of human neurological conditions are influenced by hormonal fluctuations associated with the menstrual cycle, pregnancy, the menopause and use of oral contraceptives. An appreciation of these relationships may facilitate the development of specific hormonal and anti-hormonal therapies for neurological disorders as disparate as catamenial epilepsy and acute intermittent porphyria.

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Preamble

While engaged in a neuroendocrinology fellowship at Tufts University in Boston (1987–1988), the author's mentor, Seymour Reichlin (fig. 1), to whom this paper is

dedicated, once remarked that 'neuroendocrinology is a discipline in search of a disease' [pers. commun.]. Although the clinical material encountered by a 'practicing' neuroendocrinologist may be construed as relatively limited in scope and volume, this situation changes dramatically, at least for the neurologist, when the purview of clinical neuroendocrinology is expanded to encompass the myriad influences of circulating gonadal hormones on the expression of neurological disease. In this article, we provide a general overview of fundamental sex steroid-neural interactions followed by a review of the broad spectrum of central and peripheral nervous system disorders impacted by fluctuations in the reproductive hormonal milieu. This review focuses largely on steroid-neural interactions in women, as the relatively nonfluctuating (tonic) profile of androgen secretion in men renders the impact of testicular hormones on the natural history of neurological diseases more difficult to discern.

Sex Steroid-Neural Interactions

Estrogens, progestins and androgens represent the three major classes of endogenous gonadal steroids in mammals of both sexes. The reproductive steroids are synthesized and secreted by the ovaries, testes and adrenal glands, and may also be derived from the enzyme-mediated metabolism of prohormones in extraglandular

Fig. 1. Seymour Reichlin, MD, PhD, MACP. Courtesy of Dr. Ron Lechan.

tissues. Notable examples of the latter include the aromatization of the androgens, testosterone and δ_4 -androstenedione to 17β -estradiol and estrone, respectively, in brain and adipose tissue. Approximately 98% of the plasma gonadal hormone pool is protein bound and functionally inert. The remaining 'free' fraction is highly lipophilic and readily traverses the blood-brain barrier and neuronal cell membranes. Gonadal hormones form complexes with specific receptor proteins within the cytoplasm or nucleus of the target cells. The steroid-receptor complexes induce or suppress the transcription of various genes by interacting with steroid response elements within the genes' promoter regions. Sex steroids may also impact neural functions by epigenetic modulation of cellular DNA methylation status [1]. In neurons, gonadal steroids regulate the biosynthesis of enzymes and structural proteins concerned with energy metabolism, cell membrane function, neurotransmission and hormonal sensitivity [2].

In male and female mammals, estrogen-binding neurons are concentrated in the medial amygdala, preoptic area, medial basal hypothalamus and circumventricular

organs. To a lesser extent, estrogen-binding neurons also occur in the hippocampus, basal forebrain, several thalamic nuclei, sensory regions of the brainstem and spinal cord, and the neonatal neocortex. The topographies of the estrogen, progestin and androgen target neurons exhibit considerable overlap within the mammalian neuraxis. In addition to neurons, some periventricular astrocytes also contain gonadal steroid receptors and undergo biochemical and morphological changes after hormonal exposure [2–4]. These latter observations are consistent with the fact that sex hormones may influence the growth and differentiation of certain human glial tumors (see the section Other Neoplasms).

In addition to their 'classic', receptor-mediated interactions with neural target tissues, gonadal hormones may directly or indirectly modulate neuronal discharges via rapid, nongenomic actions. An important pathway by which this occurs entails the central generation of neurosteroids from ovarian, testicular and adrenal hormone precursors. Neurosteroids can be categorized as (a) pregnane neurosteroids [e.g. allopregnanolone and allotetrahydrodeoxycorticosterone (THDOC), derived from progesterone and deoxycorticosterone, respectively], (b) androstane neurosteroids (e.g. androstanediol and etiocholanone, metabolites of testosterone) and (c) sulfated neurosteroids (e.g. pregnanolone sulfate and dehydroepiandrosterone sulfate). Neuroglial cells (astrocytes, oligodendrocytes) and certain neuronal populations are enriched for key enzymes (5α -reductase, 3α -hydroxysteroid oxidoreductase) which catalyze the interconversion of precursor hormones to neurosteroids [5–7]. Neurosteroids rapidly modulate neuronal firing by enhancing or attenuating inhibitory GABA-A receptor-mediated chloride (and other ion) conductance at the neuronal membrane. By acting as positive allosteric modulators of GABA-A receptors, allopregnanolone, THDOC and androstanediol augment GABAergic neurotransmission and thereby dampen neuronal excitability. Contrariwise, the sulfated neurosteroids may facilitate central excitation by curtailing GABAergic transmission and augmenting calcium flux through the NMDA (glutamate) receptor [5, 6]. By impacting GABAergic and glutamatergic pathways, allopregnanolone and THDOC elicit sedative-hypnotic, anticonvulsant and anxiolytic effects relevant to the pathophysiology of epilepsy (see the section Reproductive Hormones and Epilepsy) and various mood disorders. On the other hand, the net excitatory influences of pregnanolone sulfate and dehydroepiandrosterone sulfate may bolster memory functions compromised by Alzheimer disease

and related dementias (section Reproductive Hormones and Alzheimer Disease) and exacerbate anxiety disorders [5, 6, 8].

Organizational Effects

Gonadal steroids impart both organizational and activational influences within the nervous system. Organizational effects connote the irreversible differentiation of neural circuitry accruing from exposure to gonadal hormones during critical periods of brain development. A prime example of this are the roles estrogens and aromatizable androgens play in the sex-specific organization of the hypothalamic-pituitary-gonadal axis, processes which are better understood in rodents than in primates.

Rodents

In female rats and mice during the first week of life (neonatal 'critical period'), estradiol secreted by the ovaries is bound to circulating α -fetoprotein which limits the hormone's ability to traverse the blood-brain barrier. The hypothalamic pathways responsible for pituitary gonadotropin regulation are intrinsically 'female' in organization and release gonadotropin-releasing hormone (GnRH) in a pulsatile (phasic) fashion. The latter is necessary for evoking the surge in luteinizing hormone required for ovulation. α -Fetoprotein levels decline postpartum, thereby allowing ovarian estrogen to modulate the brain-pituitary axis after puberty. Testosterone administered to female rodents during the critical period does not bind to α -fetoprotein and readily accesses the developing hypothalamus. Within the immature hypothalamus, testosterone is metabolized to estradiol by the enzyme aromatase. Ironically, this estradiol 'masculinizes' the gonadotropin-regulating hypothalamic circuitry, resulting in permanent, nonpulsatile (tonic) release of GnRH and LH. In the absence of phasic LH secretion, at puberty the animal develops anovulatory sterility and multicystic ovaries. In neonatal male rodents, testosterone secreted by the testes during the critical period does not bind α -fetoprotein, aromatizes to estradiol within the hypothalamus and reorganizes the intrinsically 'female' circuitry to express 'male' (tonic) patterns of GnRH and LH secretion. The latter support normal levels of testicular androgen production at puberty. Genetic male rodents castrated at birth or treated with antiestrogens or aromatase inhibitors during the critical period will exhibit 'female' (pulsatile) patterns of GnRH-LH secretion at puberty [9]. In addition to the perinatal sensitization window, there appears to be additional, genetically and epigenetically mediated 'fine-tuning' of rodent brain masculinization/fem-

inization resulting from surges in gonadal steroid production at puberty [1, 10]. In adult rats and mice, estrogens may accelerate aging-related cytopathological changes in the mediobasal hypothalamus that may contribute to the onset of reproductive senescence [4, 11, 12].

Nonhuman Primates

The organization of the brain-pituitary-gonadal axis in primates exhibits certain fundamental differences from that of rodents: In contradistinction to rats and mice, the structural and irreversible effects of gonadal hormones on the neuroendocrine hypothalamus and other sex steroid targets within the developing monkey brain occur exclusively during the prenatal period. Moreover, circulating androgens, rather than their estrogenic metabolites, mediate the sexual differentiation of the developing monkey brain. Brain aromatase activity appears to be relatively unimportant in prenatal primates as both testosterone (an aromatizable androgen) and 5α -dihydrotestosterone (a nonaromatizable androgen) are equipotent in organizing the developing neural circuitry [13, 14]. In rhesus monkeys, exposure to prenatal androgens can both masculinize and defeminize various reproductive and nonreproductive juvenile and adult behaviors [13]. Finally, unlike the situation in rodents, fetal androgen exposure does not abrogate the positive feedback effect of estradiol on hypothalamic release of GnRH in adult primates [15].

Humans

Sexually dimorphic areas have been delineated in the human brain, including the bed nucleus of the stria terminalis, the sexually dimorphic nucleus of the preoptic area, sub-regions of the hypothalamic suprachiasmatic nucleus and several white matter tracts [16]. In a recent study of human neonates using high-resolution brain MRI and surrogate markers of intrauterine androgen exposure, structural differences between the sexes were documented in dorsolateral prefrontal, medial temporal, motor and visual cortices [17]. The authors found that while androgen exposure exerted minor gender-related influences on cortical gray matter volumes, other factors were largely responsible for cortical sexual dimorphism at this age. They concluded that 'sexual dimorphism of the [human] brain reflects the dynamic interplay of multiple mechanisms both biological (e.g. prenatal hormone production, neonatal hormone production, pubertal hormone production, direct sex-chromosome effects) and experiential (e.g. interactive behavior, exposure to physical hazards, culturally influenced lifestyle differences (ibid.))'. Nonphysio-

logical exposure to circulating gonadal hormones in utero (e.g. after maternal exposure to diethylstilbestrol) or during infancy (e.g. in children with congenital adrenal hyperplasia) may interfere with the normal development of one or more sexually dimorphic brain regions and alter the expression of gender-associated behaviors [16].

Activational Effects

'Activational effects' connote the largely reversible neurophysiological influences mediated by gonadal hormones within the mature nervous system. The latter are essential for the maintenance of normal patterns of sexual, aggressive, cognitive and autonomic behaviors and regulation of the brain-pituitary-gonadal axis. As in the case of other endocrine systems, it is often the rate of change in ambient sex hormone concentrations, rather than absolute levels per se, which determines the valence and robustness of attendant biological responses. In women of reproductive age, circulating estradiol concentrations increase during the late follicular phase of the cycle and peak just prior to ovulation. A smaller but more sustained rise in plasma 17β -estradiol occurs during the luteal phase. Progesterone levels are negligible during the follicular phase and increase considerably during the luteal phase in synchrony with the second 17β -estradiol surge. In the late luteal phase, a decline in sex hormone levels triggers the menstrual flow. In adult men, testosterone secretion by testicular Leydig cells, circulating levels of the androgen and the latter's influences on androgen target tissues are mainly 'tonic' in nature.

Germane to the central theme of this paper, hormonal changes linked to specific phases of the menstrual cycle, pregnancy, the menopause and exposure to exogenous sex hormones may impact the release and metabolism of neurotransmitters and neuromodulators and thereby give rise to, or modify, a host of neurological and neuropsychiatric conditions. All major categories of neurological affliction (vascular, metabolic, inflammatory, degenerative, etc.) are considered in this review, with emphasis on their expression in women. The article begins with disorders of the central nervous system (CNS) and progresses to those affecting peripheral nerve and muscle. In each section, common conditions encountered in clinical practice are reviewed before, and in greater detail than, the rarer entities. Nervous system disorders documented to benefit from specific hormonal and anti-hormonal therapies are discussed where appropriate. The roles of gonadal hormones in human psychiatric conditions (e.g. depression, psychosis, the premenstrual syndrome) were considered elsewhere [2].

Sex Hormones and Migraine

Epidemiology

Migraine is about three times as common in adult women as in men. Perimenstrual worsening of headaches (catamenial migraine) occurs in approximately 60% of female migraineurs. The severity or frequency of migraine attacks often diminishes with pregnancy, particularly in individuals whose headaches are associated with the menstrual cycle. Many women whose migraine condition is attenuated by gestation have relapses at the time of parturition. Breastfeeding may protect against migraine recurrence in some women. Migraine may occasionally arise or worsen during gestation or the perimenopausal period [18, 19]. Menstruation, pregnancy and the menopause may also influence cluster headache, other autonomic cephalalgias and hemicrania continua [20].

Pathophysiology

The decline in plasma estradiol (but not progesterone) in the late luteal phase plays an important role in the expression of catamenial migraine. In pregnancy, the absence of rhythmic estrogen 'withdrawal' may be responsible for the reduction in migraine activity. Estrogens may influence migraine by acting directly on vascular smooth muscle or by modulating the activity of vasoactive substances at the neurovascular junction. By altering central serotonin, prolactin, prostaglandin or opioid metabolism, perimenstrual fluctuations in circulating estrogens may also stimulate vasoregulatory elements in the hypothalamus or brainstem resulting in symptomatic alterations in cerebrovascular tone [20].

Clinical Manifestations

The clinical manifestations of hormonally associated migraine are similar to those of migraine in the general population. Women taking oral contraceptives may experience new-onset or exacerbation of migraine. Attacks tend to occur during the first few cycles (particularly on placebo days when estrogen levels are declining) and usually resolve on discontinuation of the contraceptive. Migraineurs who develop focal auras while taking oral contraceptives may be at elevated risk of infarction in the affected brain regions [20].

Treatment

Perimenstrual migraine can usually be managed with standard dietary, psychological and pharmacological modalities employed in the general migraine population. Serotonin 5-HT_{1D} (presynaptic autoinhibitory) receptor

agonists show similar efficacy in noncatamenial and menstrual migraine [21]. Late luteal phase therapy with prostaglandin inhibitors (nonsteroidal anti-inflammatory agents) and mild diuretics may be helpful in refractory cases of severe catamenial migraine. Oral contraceptives may worsen migraine and probably should not be used in the treatment of this disorder; estrogen implants and the anti-estrogen tamoxifen have yielded contradictory results. There are reports of significant symptom alleviation in women with menstrual migraine following treatment with the testosterone derivative, danazol or the dopamine agonist bromocriptine [20, 22]. To avoid risks of teratogenicity, nonpharmacological approaches to initial management of gestational migraine (e.g. relaxation training, biofeedback) should be considered. Acetaminophen with codeine or nonsteroidal anti-inflammatory agents can be used for more severe attacks. Meperidine, morphine, chlorpromazine or prednisone may need to be administered for protracted, refractory migraine (status migrainosus) in pregnancy [23]. Hormone replacement therapy (HRT) may be effective in perimenopausal migraine, but this must be weighed against the risk of developing breast cancer. In women with perimenopausal migraine and hot flashes, venlafaxine or fluoxetine may be of benefit [24].

Gonadal Hormones and Stroke

Epidemiology

Until age 85 years, men are at higher risk for atherosclerosis and ischemic stroke than women. Women exhibit 'spikes' in stroke risk in the puerperium and perimenopausally [25]. Exposure to oral contraceptives has been implicated as an important risk factor in thromboembolic cerebral infarction, cerebral venous thrombosis and subarachnoid hemorrhage. Age older than 35 years, hypertension, cigarette smoking and migraine may further increase the risk of stroke in patients on 'the Pill' [2, 26]. A recent decline in rates of thromboembolic disease among oral contraceptive users has been attributed to the lower doses of estrogen in contemporary preparations (e.g. 25–35 µg as opposed to 50–75 µg). Indeed, use of ultra-low-dose oral contraceptives (<25 µg ethinyl estradiol) may not augment stroke risk in normotensive non-smokers [27]. There are conflicting data concerning the impact of HRT on stroke incidence and severity, with reports of neutral, increased and decreased stroke risk accruing from this intervention. Importantly, several large randomized controlled studies indicated that HRT with 17β-estradiol or conjugated equine estrogen, with or

without medroxyprogesterone acetate, may worsen outcomes in women at high risk for stroke or coronary artery disease [28, 29]. Of note, men with the common ESR1 c.454-397CC variant of the estrogen receptor-α (ESRa) gene may be more susceptible to ischemic stroke than men with other ESRa genotypes after adjusting for age, smoking, diabetes, hypertension and blood lipids [30].

Pathophysiology

Sex steroids may impact atherosclerosis and attendant ischemic stroke by influencing blood coagulation cascades, platelet function, lipid profiles, inflammatory processes within the atheroma and vascular reactivity [25, 31]. Estrogen induces hypercoagulability by increasing plasma levels of fibrinogen and clotting factors VII, VIII, IX, X and XII; enhancement of platelet aggregation, and suppression of antithrombin III activity, plasminogen activating inhibitor-1 levels and fibrinolysis. Data concerning the effects of estrogens on platelet responses are conflicting. Although the platelets of women exhibit greater reactivity than those of men, hypoestrogenemia may further augment platelet responsiveness and predispose postmenopausal women to ischemic stroke [25]. Estrogen-related hypercoagulability complicating pregnancy, the puerperium and use of hormonal contraceptives may predispose to thromboembolic stroke and cerebral venous infarction. Certain inheritable prothrombotic conditions (e.g. factor V Leiden, G20210A prothrombin or methylenetetrahydrofolate reductase C677T polymorphism) further augment the risk of ischemic stroke in oral contraceptive users [32]. Sex hormones may also influence athero-occlusive vascular disease by modulating inflammatory components of the plaque. Various immune cells within or surrounding the atheroma, including B cells, T cells, dendritic cells and macrophages, express ERα, ERβ and the androgen receptor. Estrogens may protect against atherosclerosis by inhibiting stressor-induced NFκB signaling in macrophages and the synthesis of its downstream proinflammatory products IL-1β, IL-6 and TNFα [31]. Estrogens also increase dendritic cell differentiation and production of the anti-inflammatory molecules, Treg, IL-4, IL-10 and TGFβ by M2 macrophages, and decrease deposition of atherogenic oxidized low-density lipoprotein within the vascular wall. Androgens, on the other hand, may accelerate atherosclerosis by facilitating innate immune cell activation and the elaboration of proinflammatory cytokines [31, 33]. Progestins may contribute to the danger of cerebral infarction by promoting dyslipidemia, hypercoagulability and hypertension [34, 35]. The mechanisms by which female go-

nadal steroids predispose to bleeding from aneurysms and arteriovenous malformations remain controversial. Fluctuating ovarian hormone levels may compromise the integrity of cerebral arterial walls akin to their effects on endometrial spiral arteries. Gonadal hormones may also exert direct trophic influences on arteriovenous malformations analogous to their effects on other highly vascularized lesions such as gingival epulis, spider angiomas and meningiomas [20].

Clinical Manifestations

Clinically, ischemic strokes attributed to oral contraceptive use have been localized to the carotid (usually the middle cerebral artery) and vertebrobasilar systems. Neuroimaging or pathological evidence of disseminated vascular disease is usually absent in young women with oral contraceptive-related stroke. Rarely, subarachnoid hemorrhage may be cyclic in women with hormone-sensitive ectopic endometriomas of the spinal canal [20].

Treatment

Exogenous gonadal hormones should be immediately discontinued and may be prohibitive for future use in young women presenting with a stroke syndrome. The management of ischemic stroke related to gonadal hormone exposure should otherwise adhere to general guidelines and may invoke standard pharmacotherapy (antiplatelet agents, anticoagulants, fibrinolytics), interventional neuroradiology (stents) and rehabilitation. Both men and women presenting early with acute ischemic stroke may benefit from tissue plasminogen activator (tPA). However, re-canalization responses (reperfusion) following both intravenous and intra-arterial tPA administration tend to be more robust in women [36]. Although rarely encountered, periodic subarachnoid hemorrhage due to spinal canal endometriosis may respond to progestins, danazol, GnRH agonist or oophorectomy [20].

Gonadal Hormones and Movement Disorders

Chorea

Epidemiology

Pregnancy and oral contraceptive use may be complicated by the appearance of choreiform (jerky, nonrhythmic) movements involving the face and extremities. Gestational and oral contraceptive-related choreas are more prevalent in individuals with prior rheumatic fever and Sydenham's chorea [37]. Oral contraceptives may engender chorea in women with a history of congenital cya-

notic heart disease and Henoch-Schönlein purpura and amplify dyskinesias in chorea-acanthocytosis [20, 38]. Twenty percent of women may experience relapses with subsequent pregnancies. Women with oral contraceptive-related dyskinesias are more prone to develop chorea gravidarum and vice versa [20].

Pathophysiology

Altered hormonal patterns characteristic of pregnancy and ingestion of steroid contraceptives may unmask latent chorea by facilitating dopaminergic neurotransmission in basal ganglia previously injured by hypoxic or rheumatic encephalopathy [20].

Clinical Features, Diagnosis and Treatment

Women with gestational and contraceptive-related chorea may additionally exhibit fever, neuropsychiatric symptoms, dysarthria (slurred speech), pendular reflexes or limb hypotonia. Chorea gravidarum and contraceptive-related dyskinesias usually resolve by parturition or after discontinuation of the medication, respectively. In patients with suspected chorea gravidarum, appropriate clinical and laboratory investigations may be indicated to exclude other etiologies, such as hyperthyroidism, rheumatic fever, Wilson disease or systemic lupus erythematosus. As chorea gravidarum is usually self-limited, abortion or premature delivery is rarely required. In severe cases, neuroleptics (dopamine antagonists) may afford symptomatic relief. Individuals with a history of chorea gravidarum or contraceptive-induced dyskinesias should probably avoid further exposure to estrogen-containing medications [20].

Parkinsonism

Epidemiology

Idiopathic Parkinson disease is an aging-related neurodegenerative disorder that is more common in men than women with an incidence ratio of approximately 1.5:1 [39]. A large, recent study comparing drug-naïve men and women with early Parkinson disease matched for the degree of motor impairment revealed significant gender disparities in the prevalence of nonmotor symptoms: deficits in olfaction and in certain cognitive domains (global, memory, visuospatial) were more severe in men, whereas trait anxiety was greater in women [40]. Data concerning the impact of reproductive hormones on parkinsonism are conflicted. Early anecdotal reports suggested that exposure to exogenous estrogen may exacerbate idiopathic and neuroleptic-induced parkinsonism. However, more recent studies of premenopausal women

with idiopathic Parkinson disease documented perimenstrual worsening of motor symptoms when estrogen titers were falling [20, 41]. Postmenopausal HRT is variably reported as beneficial [42, 43], detrimental [44] or inconsequential [45] in women with Parkinson disease. Early menopause (natural or surgical) has been touted as a risk factor for the development of Parkinson disease [46, 47] which may be mitigated by postmenopausal estrogen replacement [47]. Conversely, no evidence of a salutary effect of estrogen on the risk of developing Parkinson disease could be adduced in a large prospective study [48]. In one case-control study, steroid contraception emerged as a susceptibility factor for the disease with an adjusted odds ratio of 3.27 (95% CI: 1.24–8.59; $p = 0.01$) [49].

Pathophysiology

Clinical and experimental data indicate that estrogens may influence motor manifestations of parkinsonism by modulating dopaminergic tone within the nigrostriatum. But whether the estrogenic influences on dopaminergic neurotransmission in this disease are predominantly stimulatory or inhibitory remains uncertain [2]. In animal models of Parkinson disease, the neurosteroid allopregnanolone enhances neurogenesis in the substantia nigra, modulates dopamine release and improves motor control [8]. The latter findings may have clinical significance given that allopregnanolone concentrations are reportedly low in the plasma and cerebrospinal fluid of patients with idiopathic Parkinson disease [50, 51].

Treatment

Hormonal interventions are rarely indicated in the management of parkinsonism impacted by gonadal steroid fluctuations. In light of the data reviewed in the preceding section, Irwin et al. [8] have advocated clinical trials to investigate the potential neuroprotective and therapeutic benefits of allopregnanolone in subjects with Parkinson disease.

Wilson Disease

Epidemiology

Wilson disease is a rare inborn error of copper metabolism that is characterized by decreased blood ceruloplasmin levels, hepatic cirrhosis, corneal copper deposition (Kayser-Fleischer rings) and degenerative changes in the basal ganglia [20].

Pathophysiology

Movement disorders, seizures and psychosis result from the toxic effects of excessive copper deposition in

neural tissues. Serum ceruloplasmin and copper levels may increase during pregnancy and after administration of steroid contraceptives in normal individuals and in patients with Wilson disease [20].

Diagnosis and Treatment

In women with Wilson disease, diagnosis may be delayed by ‘normalization’ of ceruloplasmin levels resulting from exposure to steroid contraceptives. This false normalization of blood ceruloplasmin concentrations confers no therapeutic advantage, and may in fact be associated with neurological deterioration (abnormal movements, seizures, psychosis) in some individuals [20]. It remains unknown whether gonadal hormones similarly raise blood ceruloplasmin titers in other conditions featuring low levels of the protein, such as acquired copper deficiency or hereditary hypoceruloplasminemia [52].

Other Movement Disorders

Fluctuating gonadal hormone levels have also been reported to influence symptoms in patients suffering from Tourette syndrome, tardive dyskinesia, familial episodic ataxia, hereditary and posthypoxic myoclonus, dominantly inherited myoclonic dystonia, hemiballismus, drop attacks and the neuroleptic malignant syndrome [20, 53, 54].

Reproductive Hormones and Epilepsy

Epidemiology

Seizure disorders and their treatments may disrupt normal reproductive processes. Hypogonadotropic hypogonadism, the polycystic ovary syndrome and hyposexuality may be due to aberrant limbic discharges in patients with temporal lobe epilepsy [20]. Oral contraceptive failure occurs with increased frequency in epileptic women exposed to phenobarbital, primidone, phenytoin, carbamazepine and ethosuximide [55]. Topiramate and felbamate may influence gonadal hormone pharmacokinetics and thereby compromise contraceptive efficacy [56]. Valproic acid does not interfere with the Pill’s efficacy but may cause hyperandrogenism and polycystic ovaries [57]. Failure of oral contraception does not appear to be a concern in women taking vigabatrin, gabapentin, levetiracetam, clobazam, zonisamide or lamotrigine [55, 58, 59]. Tiagabine may elicit breakthrough bleeding, but the overall impact of this drug on gonadal steroid metabolism is thought to be minimal [60].

The natural history of epilepsy and its management may be greatly influenced by specific phases of the reproductive cycle and exposure to hormonal contraceptives. Various seizure disorders may worsen premenstrually (catamenial epilepsy), at ovulation or during pregnancy. Menstrual irregularity at ages 18–22 years was associated with an increased risk of epilepsy (RR 1.67, 95% CI 1.12–2.51) in a large study [61]. The influences of the menstrual cycle and of oral contraceptive preparations on anticonvulsant disposition appear to be of minor clinical significance. On the other hand, gestational plasma concentrations of phenobarbital, phenytoin and valproic acid may decrease by 30–40% percent of prepregnancy levels, with a lesser decline in carbamazepine. Primidone concentrations remain fairly stable during pregnancy, but the level of primidone-derived phenobarbital may be diminished [20].

Pathophysiology

Most anticonvulsants implicated in oral contraceptive failure induce the hepatic cytochrome P450 microsomal enzyme system, which, in turn, accelerates catabolism of reproductive steroids. Anticonvulsants may also (a) stimulate the production of sex hormone-binding globulins, resulting in diminished concentrations of circulating free (active) hormone and (b) facilitate the clearance of gonadal hormones by influencing their sulfate conjugation and glucuronidation in the liver and gut [20].

Estrogens and progestins have epileptogenic and anticonvulsant properties, respectively. Estrogens and the sulfated neurosteroids (see the section Sex Steroid-Neural Interactions) enhance glutamatergic and attenuate GABAergic neurotransmission, favoring epileptogenesis; progesterone and certain pregnane and androstane neurosteroids have the opposite effects [6, 62]. Perimenstrual seizure activity may be precipitated by rising estrogen:progesterone ratios during the late luteal phase. Conceivably, elevated estrogen:progesterone ratios characteristic of the polycystic ovary syndrome may explain the relatively frequent association of this infertility condition with temporal lobe epilepsy. Estrogen-progestin contraceptives do not significantly worsen seizure control in women with epilepsy [55]. Regarding gestational epilepsy, inadequate anticonvulsant levels, sleep deprivation and stress may be more salient than direct hormonal epileptogenesis. Decreased drug compliance, bioavailability, an increased volume of distribution and enhanced metabolic clearance contribute to the fall in anticonvulsant levels during pregnancy [63].

Treatment

Approaches to the management of catamenial epilepsy include (1) premenstrual or periovulatory supplementation of anticonvulsant doses or addition of an adjunctive anti-epileptic drug (e.g. clobazam); (2) cyclic administration of a mild diuretic such as acetazolamide (which has weak anticonvulsant activity) and (3) progesterone supplementation by mouth or suppository [64, 65]. More frequent monitoring of anti-epileptic drug levels during pregnancy is prudent, with dosage adjustments (usually increments) implemented as necessary. Early-phase human clinical trials have been conducted assessing the anticonvulsant effects of the allopregnanolone analog ganaxolone (3 α -hydroxy-3 β -methyl-5 α -pregnane-20-one). Ganaxolone is a positive allosteric modulator of GABA-A receptors (see the section Sex Steroid-Neural Interactions) which has shown promise in animal models of epilepsy. In randomized, placebo-controlled trials, the synthetic neurosteroid diminished seizure activity in adults with drug-resistant partial-onset seizures and children with refractory infantile spasms. Ganaxolone was safe and well-tolerated, with dizziness and fatigue being the most frequently reported adverse effects [66–68]. Importantly, ganaxolone lacks hormonal activity and therefore does not expose patients to the potential risks of progestin therapy [69].

Gonadal Hormones and Multiple Sclerosis

Epidemiology

Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the CNS that is most often diagnosed in men and women during their reproductive years. An association between MS and certain *ESR1* gene polymorphisms has been documented in some studies [70, 71], but not others [72]. Contrary to earlier medical dogma, the overall impact of one or more pregnancies on MS-related morbidity is minimal [73]. There is a tendency for MS to worsen during the first 3 postpartum months that is counterbalanced by amelioration of disease activity in the third trimester [74]. Oral contraceptive exposure may delay the onset of MS but does not appear to influence the risk of developing the disease [75].

Pathophysiology

Attenuation of third-trimester disease activity in MS (and other immune-mediated conditions) is likely due to relative maternal immunosuppression that serves to obviate rejection of the semi-allogenic fetus. Circulating fac-

tors that may mediate gestational immunosuppression include estradiol, progesterone, α -fetoprotein, pregnancy-associated glycoprotein, human chorionic gonadotropin, human placental lactogen, 1,25-dihydroxyvitamin D₃, cortisol and interleukin-10 [20, 26]. Neurosteroids have been implicated in the pathogenesis of MS inasmuch as (a) allopregnanolone may be deficient in the white matter of MS patients and (b) allopregnanolone stimulates neuronogenesis, oligodendroglioneogenesis and myelin formation, suppresses neuroinflammation and modulates the innate immune response [8, 76].

Treatment

MS attacks in pregnancy can be treated with intravenous steroids. Interferons should be discontinued at least 3 months before planned conception and should not be administered during pregnancy or while breastfeeding [20]. In an Israeli study, none of 14 pregnant women with relapsing-remitting MS who were treated with prophylactic intravenous immunoglobulins immediately after delivery exhibited disease relapse within the subsequent 6 months [77]. Preliminary reports of potentially beneficial effects of oral estriol in women with MS and transdermal testosterone in men with the disease [78] require confirmation.

Reproductive Hormones and Alzheimer Disease

Epidemiology

Alzheimer disease is a common dementing illness characterized by progressive neuronal degeneration, gliosis, marked depletion of acetylcholine and other neurotransmitter disturbances and the accumulation of senile (amyloid) plaques and neurofibrillary tangles in discrete regions of the basal forebrain, hippocampus and association cortex [79]. Early clinical investigations suggested that estrogen replacement therapy may enhance cognitive performance (especially attention, verbal memory and language function) and increase responsiveness to acetylcholinesterase inhibitors in menopausal women with Alzheimer disease [80–84]. Furthermore, postmenopausal HRT was associated with a significantly reduced risk of developing Alzheimer disease in several case-controlled studies [85–87], in a meta-analysis of 12 observational studies [88] and in initial prospective studies [89, 90]. There was also some indication of enhanced cognition in elderly men with Alzheimer disease or mild cognitive impairment treated with estrogen [91] or testosterone [92, 93]. Despite this initial optimism, cognitive

function scores were no different in women with coronary artery disease who received estrogen and progestin than in placebo-treated controls in the randomized Heart and Estrogen/Progestin Replacement Study (HERS) [94]. Moreover, in the large Women's Health Initiative Memory Study (WHIMS), the hazard ratios for development of dementia were 1.49 for women randomized to receive 0.625 mg conjugated equine estrogen and 2.05 for those receiving 0.625 mg estrogen plus 2.5 mg medroxyprogesterone acetate relative to placebo-treated controls [95].

Pathophysiology

Data amassed from fundamental studies suggest that estrogens could theoretically improve cognition in Alzheimer disease by (a) promoting neuritic arborization and dendritic spine formation, (b) providing trophic support for cholinergic neurons and *N*-methyl-D-aspartate receptors, (c) attenuating β -amyloid deposition, neuroinflammatory responses and oxidative neural damage and (d) improving cerebral blood flow and glucose utilization [20]. Downmodulation of brain β -amyloid deposition by androgen exposure has also been reported [96]. Neurosteroids may also contribute to cognitive health insofar as allopregnanolone increases hippocampal neurogenesis, dampens microglial activation (neuroinflammation), decreases β -amyloid pathology and reverses learning and memory deficits in animal models of Alzheimer disease [8]. Moreover, there are reports of reduced levels of allopregnanolone in the prefrontal cortex and subnormal concentrations of DHEA-S in the plasma and cerebrospinal fluid of Alzheimer subjects [6].

Treatment

On the basis of the disappointing data derived from large, randomized, placebo-controlled trials (see above), the third Canadian Consensus Conference for the Diagnosis and Treatment of Dementia (2006) recommended against the use of estrogen/progestin replacement therapy for reducing the risk of dementia in postmenopausal women. However, some have recently argued that the large therapeutic trials may have missed a critical perimenopausal 'window' during which HRT may protect against the development of Alzheimer disease [97, 98]. Of note, administration of pregnanolone ameliorated cognitive deficits in individuals with schizophrenia [99]. This observation, in conjunction with the preclinical and human biochemical data summarized in the preceding section, raises the possibility that exogenous neurosteroids may preserve or enhance cognition in patients with Alzheimer disease and other neurodegenerative de-

mentias [8]. In one small, placebo-controlled study, 6 months of treatment with DHEA failed to confer significant cognitive benefits in patients with Alzheimer disease [100].

Gonadal Hormones and Sleep Disorders

Epidemiology

In women, sleep architecture is impacted by puberty, menstruation, pregnancy and the menopause. Overall, sleep-associated complaints are more prevalent in women than men. Gender differences in sleep patterns become apparent after puberty and may contribute to the risk of developing sleep disorders [101]. For example, insomnia is more common in women than men, with the prevalence between the sexes diverging with advancing age. Restless legs syndrome slightly favors women, whereas obstructive sleep apnea and rapid eye movement sleep behavior disorder occur more frequently in men [101, 102].

Pathophysiology

The mechanisms by which altered gonadal hormone concentrations and their influences on neural targets within the diencephalon and brain stem impact human sleep physiology remain poorly understood. Hypogonadism in women may disrupt normal sleep architecture by increasing mean sleep latencies, curtailing epochs of rapid-eye-movement sleep and facilitating nocturnal movement arousals [103]. The preponderance of obstructive sleep apnea in men may be dependent not only on disparities in the gonadal steroid milieu but also on sex differences in local neuromuscular reflexes and central ventilatory control [101].

Treatment

Combined estrogen-progesterone therapy attenuated breathing irregularities, periodic limb movements, nocturnal arousals, hot flashes and bruxism (teeth grinding) in a study involving 33 postmenopausal women [104]. In patients with central sleep apnea, progestins may alleviate hypoventilation by providing stimulatory drive to brain-stem respiratory centers. The administration of progesterone to healthy men decreases vigilance during wakefulness, an effect possibly mediated by the GABAergic agonists, pregnanolone and allopregnanolone [105]. In one report, obstructive sleep apnea resolved in a non-obese woman following excision of a benign, testosterone-producing ovarian tumor [106].

Gonadal Hormones and Nervous System Neoplasms

Meningiomas

Epidemiology

Meningeal tumors are more prevalent in women than men of reproductive age. Meningiomas may occur more commonly in women who are obese or have hormone-dependent breast carcinoma [20]. An increase in the incidence of meningioma in women receiving HRT was reported in a large Finnish study [107].

Pathophysiology

A significant proportion of human meningioma specimens express progesterin- and, to a lesser extent, estrogen- and androgen-binding proteins. These steroid-binding proteins likely mediate the effects of gonadal hormones on meningioma growth and differentiation. Higher circulating estrogen levels derived from the aromatization of androstenedione to estrone in adipocytes may explain the higher prevalence of meningiomas in obese individuals [20]. Perimenstrual and gestational changes in tumor size may be due to direct trophic effects of gonadal hormones on meningioma cells, steroid-induced fluid retention by the tumor or increased vascular engorgement of the lesion [108].

Clinical Manifestations and Treatment

Women may experience exacerbations of symptoms related to meningiomas in the luteal phase of the menstrual cycle. There is also clinical and radiological evidence for the rapid growth of meningiomas during pregnancy, followed by their spontaneous regression postpartum [109]. Progesterone receptor-negative meningiomas tend to display greater mitotic indices and necrosis [110], a higher propensity for brain invasiveness and shorter disease-free intervals [111]. The antiprogesterin agent RU486 has been reported to stabilize growth or induce regression of meningiomas. However, patients on long-term RU486 therapy may require glucocorticoid replacement to offset the drug's anti-glucocorticoid effects [112]. Although meningiomas may be encountered more frequently in women receiving HRT [107], this observation should not influence the practice of HRT as the overall prevalence of these tumors remains very low in this population [113].

Other Neoplasms

Astrocytomas may selectively bind estrogens, progestins or androgens. In astroglial neoplasms, expression levels of estrogen receptor- β may vary inversely with the

degree of histopathological dedifferentiation and malignant behavior [114]. Astrocytomas have been reported to expand during pregnancy and regress in the puerperium. Clinical and radiological stabilization of astrocytomas and glioblastoma multiforme has been reported in some patients following treatment with the anti-estrogen tamoxifen [115–117]. In this regard, the radiosensitizing effects of tamoxifen or its inhibitory effects on protein kinase c activity may be more important than its anti-estrogenic properties [20]. The presence of gonadal steroid receptors or biological responsiveness to reproductive hormones has also been described in cases of pituitary adenomas, acoustic neuromas, oligodendrogliomas, anaplastic ependymomas, lymphomas, hemangioblastomas, primitive neuroectodermal tumors and breast cancer metastases to the neuraxis [20, 118–120].

Gonadal Hormones and Neuromuscular Disorders

The Porphyrias

Pathophysiology, Clinical Manifestations and Diagnosis

The porphyrias feature enhanced production of porphyrin precursors and porphyrins accruing from enzymatic defects in heme biosynthesis. Sensorimotor and autonomic neuropathies, neuropsychiatric symptoms and seizures are frequent neurological manifestations of certain porphyrias. Estradiol and other steroid hormones may trigger porphyric crises by inducing the heme biosynthetic enzyme δ -aminolevulinic acid synthase. In women with acute intermittent porphyria, cyclical attacks of neuropathy and other neurological symptoms may occur during the late luteal phase or at ovulation. Diagnosis is aided by measurement of blood or urinary porphyrins and confirmed by genetic testing [20, 26].

Treatment

Chronic administration of GnRH agonists, such as leuprolide or D-His, downregulates gonadotrope GnRH receptors, resulting in long-term suppression of the pituitary-ovarian axis. In an early report [121], complete remission of catamenial acute intermittent porphyria was observed during 8 months of D-His treatment. Subsequent cases of perimenstrual acute intermittent porphyria and hereditary coproporphyria also exhibited beneficial responses to GnRH agonist therapy. Breast tissue atrophy, hot flashes and bone demineralization may complicate prolonged treatment with GnRH analogs [20, 122]. It may be prudent for asymptomatic relatives of pa-

tients with genetic porphyrias to avoid exposure to oral contraceptives.

Catamenial Sciatica

Pathophysiology, Clinical Manifestations and Diagnosis

Ectopic endometrial tissue (endometriosis) is sensitive to steroid hormones and exhibits sloughing and hemorrhaging during menses. Endometriosis may cause back or pelvic pain by invading lumbar vertebrae, the lumbosacral plexus or the sciatic nerve sheath. The latter elicits radicular pain that usually begins several days before the onset of menses and may continue until cessation of flow (catamenial sciatica). Leg weakness, numbness and loss of ankle reflexes may accompany the pain. Unlike discogenic radiculopathy, neuroimaging in endometriotic sciatica is generally unremarkable. Evidence of endometriosis elsewhere may or may not be apparent. Surgical exploration of the sciatic nerve may be required for diagnosis. The nerve appears blue in positive cases and incision of the sheath reveals a dark, hemorrhagic fluid. Characteristic glandular elements are observed at histopathology [26, 123].

Treatment

Symptoms of endometriotic sciatica are less likely to remit with bed rest than those of discogenic radiculopathy. The former may improve dramatically with standard therapy for endometriosis, including progestins, danazol, GnRH agonist or (in refractory cases) oophorectomy [20, 124].

Other Neuromuscular Conditions

Endogenous and administered gonadal steroids (mainly estrogens) may impact the natural history of the carpal tunnel syndrome, Bell's palsy and recurrent brachial plexopathy. The mechanism(s) underlying these effects may involve hormone-related soft tissue swelling and attendant nerve compression. Dysfunction of testicular peritubular myoid cells may contribute to the hypergonadotropic hypogonadism and impotence in men with myotonic dystrophy [125]. Hyperestrogenemia may occur in male patients with amyotrophic lateral sclerosis, bulbospinal muscular atrophy (Kennedy's syndrome), Kugelberg-Welander disease, Duchenne muscular dystrophy and POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes associated with plasma cell dyscrasias). Whether the hyperestrogenemia plays any significant role in the pathogenesis of these neuromuscular disorders remains unclear [2].

High-dose testosterone was reported to ameliorate symptoms in a patient with bulbospinal muscular atrophy. Attenuation of the toxic gain of function ascribed to the mutated androgen receptor in this condition was invoked as a putative mechanism [126].

Conclusions

Gonadal hormones exert potent organizational and activational effects within the mammalian neuraxis and influence a wide spectrum of normal and abnormal neurological functions. The former may act directly on salient neural pathways or serve as precursors of bioactive neurosteroids. Relationships between endogenous and exogenous sex hormones and many neurological disorders, such as stroke, chorea, porphyria, epilepsy and migraine, are well established. In other conditions, including various movement disorders, CNS tumors, sleep apnea and MS, this relationship has not been confirmed but appears likely in the light of rapidly accumulating epidemiological, clinical and neuroimaging data. Changes in plasma reproductive hormone concentrations may also

modulate the expression of diverse psychiatric states, including depression, psychosis, the premenstrual syndrome and anorexia nervosa [2]. Given the robust and fairly ubiquitous nature of steroid-neural interactions in humans, clinical inquiry into potential symptom fluctuations associated with the menstrual cycle, pregnancy, menopause and hormonal contraceptive exposure in women with neurological and psychiatric illness should become a matter of routine. Further delineation of the molecular mechanisms mediating the trophic and adverse effects of sex steroids on neurological well-being should inform future development of novel hormonal and anti-hormonal therapeutics for managing many of the afflictions discussed in this review.

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