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Hormones and Epilepsy

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Few areas of epileptology have been more intriguing and yet as poorly understood as that of the role of hormones. New knowledge of hormonal effects on brain development and neuronal activity is leading to an improved understanding of the role of hormones in epilepsy, as well as new prospects for pharmacotherapy. This review will consider recent developments in the understanding of hormone actions during brain development, catamenial epilepsy, and oral contraceptives, neuroendocrine dysfunction in temporal lobe epilepsy, and endocrine function following seizures and with antiepileptic treatment.

HORMONES IN BRAIN DEVELOPMENT

Hormonal regulation is critical for normal brain development and may play important roles in the development of clinical seizure disorders. For example, early in life, a deficiency of thyroid hormone is associated with delay in neuronal and glial differentiation in rats, whereas corticosteroids retard dendritic development. A lack of either growth hormone or thyroid hormone leads to a failure of myelin formation. Hormonal deficiencies may result from nutritional deprivation, brain damage from an intracerebral insult, or an endogenous metabolic defect. These may lead, in turn, to deficient hypothalamic stimulation of hormone-releasing factors and defective systemic feedback regulation of the limbic system and hypothalamus.[34]

Research in the field of steroid hormone action has begun to elucidate the role of intracellular receptor sites that transport hormone into the cell nucleus and trigger the expression of genetic information in the form of altered protein synthesis. Such mechanisms have been evaluated for the five major classes of steroid hormones: estrogen, progestins, androgens, glucocorticoids, and mineralocorticoids.[21] In addition, steroid hormones may act directly by altering permeability to neurotransmitters or their precursors and functioning of neurotransmitter receptor sites.

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Particular interest has been directed toward the marked ability of progesterone and its derivatives to lower seizure thresholds that have been observed clinically over recent years.[37, 38] Holmes[15, 16] has demonstrated a marked effect of progesterone in the inhibition of kindling of seizures in immature animals but no effect on seizures in adults. Progestin receptors in the brain are widespread and show specific patterns in cortex and pituitary during fetal and postnatal development.[17] Some of these receptors are regulated by estrogen and appear to be localized to the hypothalamus, whereas those in the midbrain and cerebral cortex appear to be insensitive to estrogen.[27] This latter group may be especially important for the control of "centrencephalic" seizures by the use of progestational agents.

Hormones have marked indirect effects on seizure thresholds; for example, seizures are seen in hypocalcemia with hypoparathyroidism and hypoglycemia with hyperinsulinemia. Although endocrinopathies in general are not epileptogenic, seizures can result from indirect hormonal effects on the brain and may also exacerbate seizures in patients with pre-existing electroencephalographic abnormalities (for example, in hypoadrenalism, as well as hypo- and hyperthyroidism). Although its mechanism of action is unclear, ACTH lowers seizure thresholds in older children and adults but ameliorates seizures in childhood and is particularly effective in infantile spasms. Several investigators have utilized portions of the ACTH molecule in order to treat infantile spasms without the hormonal side effects of ACTH.[26] There is clearly age-dependent variability in the responses of neurons to hormones that may be mediated in part by changes in receptors for hormones as well as for neurotransmitters and opiates.[31]

CATAMENIAL EPILEPSY

The exacerbation of seizures before or during menstruation generally has been correlated with the rapid fall of progesterone and the relative decrease in the progesterone to estrogen ratio. In a recent review of catamenial epilepsy, Nemark and Penry[24] emphasized the need for a consistent definition of the disorder.

Several investigators have found altered anticonvulsant binding during menses. Changes in phenytoin pharmacokinetics have been described by Shavit et al.[30] who found that serum phenytoin falls during menses, associated with increased clearance of the drug. If lower drug levels are found during menses, increased doses of anticonvulsants may improve seizure control.

Although there is not widespread agreement on the definition or the causes of catamenial epilepsy, in clinical practice, a large number of young women with epilepsy have exacerbation of seizures during menses. Therapy for these patients is difficult because few systematic therapeutic trials have been carried out and there are therefore no established guidelines. Each patient must be treated with careful attention to her individual needs, taking her epilepsy as well as her endocrine status into consideration. For many of these patients it is advisable to coordinate care with an obstetrician-gynecologist or endocrinologist.

Table 1. *Treatment of Catamenial Epilepsy*

DRUG	DOSE
Acetazolamide (Diamox, Lederle)	125–500 mg daily, 5–7 days before expected onset of menses until cessation of bleeding[2]
*Medroxyprogesterone acetate (MPA) (oral; Provera, Upjohn)	10 mg twice a day to four times a day[20, 38]
*MPA (intramuscular; Depo-Provera)	120–150 mg every 6–12 weeks[20, 38]
Megestrol acetate (oral; Megace, Mead Johnson)	40 mg once a day[23]

*Investigational; see text regarding cautions in use of MPA. Gynecologic consultation and informed consent are advisable.

Table 1 describes several possible approaches to the patient with catamenial epilepsy. Although the use of acetazolamide (Diamox) has generally been advocated for the treatment of catamenial epilepsy,[2] most authors have not found it to be helpful over long periods of time. Following early anecdotal reports of successful treatment of menstrual epilepsy using progesterone[38] or oral contraceptives,[13] several investigators have been using progesterone in larger groups of patients. One study found an oral preparation of norethisterone to be ineffective in nine patients.[6] Mattson has found a significant reduction in seizure frequency in seven of 11 women using continuous oral medroxyprogesterone.[20] Bäckström et al. showed that intravenous progesterone infusion reduced the spike frequency on electroencephalogram (EEG) in four of seven patients, and the effect was most marked in patients with low progesterone-binding capacity.[3] The nonhormonal treatment of catamenial epilepsy by a benzodiazepine, clobazam, also appears promising.[10]

Medroxyprogesterone acetate (MPA, Provera) has been used worldwide as a contraceptive and by gynecologists to treat ovulatory dysfunction, endometriosis, and anovulatory bleeding. Although MPA would appear to be a logical choice for the treatment of catamenial epilepsy, and the drug at one point was believed to be safe, a special panel recently advised the FDA not to approve the drug as a general contraceptive.[33] Their decision was attributed to poor experimental designs and inconclusive results in the testing of MPA. Potential carcinogenesis of MPA remains an open question. In addition, some patients have had problems with breakthrough bleeding, and there are uncertainties about correct drug levels. Therefore, MPA is currently approved by the FDA only for the treatment of endometrial cancer. The emerging experimental and clinical evidence of the beneficial effects of progesterone and progestins in preventing and ameliorating seizures should stimulate further studies of MPA and new compounds that may be more specific for progestin receptors in the nervous system.

"THE PILL"

Oral contraceptive agents vary in their effects on the frequency of seizures in individual patients. "The pill" can be used by most epileptics,

Table 2. *Steroid Content Per Tablet of Some Oral Contraceptives*

>50 μg Estrogen	*Estrogen (μg)*		*Progestogen (mg)*	
Enovid 5 mg (Searle)	mestranol	75	norethynodrel	5.0
Norinyl 2 mg (Syntex)	mestranol	100	norethindrone	2.0
Ortho-Novum 1/80 (Ortho)	mestranol	80	norethindrone	1.0
50 μg Estrogen				
Norlestrin 2.5/50 (Parke-Davis)	ethinyl estradiol	50	norethindrone acetate	2.5
Ovcon-50 (Mead Johnson)	ethinyl estradiol	50	norethindrone	1.0
Ovral (Wyeth)	ethinyl estradiol	50	norgestrel	0.5
< 50 μg Estrogen				
Loestrin 1.5/30 (Parke-Davis)	ethinyl estradiol	30	norethindrone acetate	1.5
Lo/Ovral (Wyeth)	ethinyl estradiol	30	norgestrel	0.3
Ortho-Novum 1/35 (Ortho)	ethinyl estradiol	35	norethindrone	1.0
Progestogen Only				
Micronor (Ortho)	—		norethindrone	0.35
Nor-Q.D. (Syntex)	—		norethindrone	0.35
Ovrette (Wyeth)	—		norgestrel	0.075

(*Adapted from* Murad, F., and Haynes, R. C. Jr.: Estrogens and progestins. *In* Gilman, A. G., Goodman, L. S., and Gilman, A. (eds.): The Pharmacological Basis of Therapeutics. Ed. 6. New York, Macmillan Publishing Co., 1980, pages 1420–1447.)

although exacerbation of seizures may occur in some patients, particularly during withdrawal bleeding.[9] As stated, there is a fair amount of evidence to suggest that estrogens aggravate cortical irritability, whereas progestins ameliorate it. As most commonly used oral contraceptives are combinations of differing amounts of these two hormones, there may be certain agents which are more beneficial to epileptic patients than others; however, this has not been studied systematically. In addition, most combination pills are taken in a 21 days-on, 7 days-off cycle, which mimics natural hormonal withdrawal prior to menses but may induce seizure activity during the withdrawal in some patients.

Table 2 lists some of the commonly available oral contraceptives in four categories according to their steroid content. Those first introduced contained greater than 50 μg estrogen per tablet, as well as higher doses of progestogen. Complications are more common with these agents, including hemorrhagic and thromboembolic stroke, deep vein thrombosis, and pulmonary embolism.[23] Lower doses of estrogen (50 μg or less) in the newer agents are associated with fewer serious side effects but are more likely to produce withdrawal bleeding. In spite of the risks of these and other possible complications from use of "the pill," they are outweighed in most patients by the increased risks of pregnancy, which is frequently accompanied by exacerbation of seizures in women with severe epilepsy.[9]

Progestin-only agents (Mini-pills; see Table 2) may be preferable in epileptic women for control of seizures, as a dose of progestin is taken every day throughout the cycle. They are not as effective for contraception as those agents that contain estrogen, and like all oral contraceptives, may have further reduced contraceptive efficacy in epileptics owing to competitive protein binding by anticonvulsants.[19] Additional contraceptive measures may therefore be necessary in the patient who is sexually active.

Although use of "the pill" to control seizures has not been established,

oral contraceptives may be helpful in controlling seizures in women whose seizures are refractory to anticonvulsants even with the addition of acetazolamide prior to and during menses. "The pill" may be preferred over medroxyprogesterone acetate or megestrol acetate in patients who have mild or moderate difficulty with seizure control and in whom side effects of MPA may be undesirable. First choice for an oral contraceptive might be one of the progestin-only agents and if anovulatory bleeding occurs, another agent containing less than 50 μg of estrogen should be tried. In choosing combination pills, preference should be given to those that contain relatively larger amounts of progestogen relative to estrogen in each group (see Table 2). Further trials of combination agents in the 50- and greater-than-50-μg estrogen group may be warranted, depending on the patient's response; however, it should be kept in mind that more potential side effects may occur with increasing doses of estrogen.

NEUROENDOCRINE DYSFUNCTION IN TEMPORAL LOBE EPILEPSY

Several important neuroendocrine systems have been studied recently in patients with temporal lobe epilepsy. Elevated ACTH and ACTH secretory rates in patients with temporal lobe epilepsy have been reported by Gallagher et al.[12] They showed that ACTH levels and secretory rates returned to normal following temporal lobectomy in 11 patients, but they did not correlate to the degree of improved seizure control. Seizure patients also had significantly higher ACTH levels than patients with pseudoseizures, although cortisol levels and secretory rates were similar (which may have resulted from anticonvulsant medications in the pseudoseizure group). Cortisol levels and secretory rates were greater in seizure patients than controls. In contrast to seizure patients in whom secretory patterns of ACTH and cortisol (measured every 5 minutes) were frequent and showed irregular and high peaks, normal subjects and postoperative patients had smooth patterns with smaller fluctuations. Thus increased stimuli for release of ACTH and other hormones and peptides appear to be transmitted via limbic pathways during seizure activity.

The relationships between behavioral and neuroendocrine dysfunction have been evaluated in patients with temporal lobe epilepsy. Spark et al.[32] found unrecognized temporal lobe epilepsy in 11 of 16 hyposexual men, six of whom had neuroendocrine findings including hyperprolactinemia, subnormal testosterone, or blunted LH response to LHRH. Two men became normal on anticonvulsant therapy alone.

Herzog et al.[14] measured the response of serum LH to intravenous LHRH infusion in seven patients with temporal lobe epilepsy and normal controls. All four of the men with temporal lobe epilepsy had decreased LH response curves, whereas the three women showed a range of responses either well above or below the normal range. These results suggest dysfunction of the hypothalamic-pituitary axis, even though other neuroendocrine functions were normal in these patients. The authors raised the possibility that neuroendocrine treatment might benefit these patients.

Sex hormones, sexual activity, and plasma anticonvulsant levels were measured in 72 male patients by Toone et al.[35] All patients were on multiple drug regimens. They found no significant correlations for phenytoin or phenobarbital, but carbamazepine and prolactin levels were correlated. Sodium valproate correlated significantly with total testosterone and LH. Sexual activity appeared to be diminished in relation to reduced free testosterone. There was no correlation of plasma anticonvulsant levels with sexual behavior measures. Rodin et al.[29] found elevated FSH, LH, and prolactin in 33 male epileptics; mean testosterone levels were lower in a subgroup who reported symptoms of hyposexuality compared with the other patients.

These studies emphasize the importance of neuroendocrine evaluation of male as well as female patients with sexual dysfunction. The proportion of adult epileptics with sexual dysfunction has not been determined, nor is there an estimate of the percentage of patients with sexual dysfunction who may have temporal lobe epilepsy. However, the studies offer new approaches to the evaluation and treatment of these patients.

ENDOCRINE FUNCTION FOLLOWING SEIZURES

Elevations of serum prolactin following generalized tonic-clonic as well as complex partial seizures have been described.[1, 7, 8, 28, 36] Although marked postictal prolactin elevation appears to be a sensitive indicator of seizures within 15 to 30 minutes following the ictus, not all patients show this elevation, and a normal prolactin level, therefore, does not exclude the possibility of a seizure. The findings of elevated LH as well as FSH have not been found uniformly by different authors. Elevated ACTH beta-endorphin, beta-lipotropin, vasopressin, and a later increase in cortisol following seizures were reported by Aminoff et al.[1] Nocturnal elevation of prolactin (but not cortisol) is greater in patients with partial complex seizures than controls, which suggests that the hyperprolactinemia in these patients is not stress related.[22]

The rise in prolactin following a seizure suggests a possible relationship between temporal lobe dysfunction and psychopathology in patients with complex partial seizures. Electrical stimulation of the amygdala in humans through chronically implanted electrodes produced a significant rise in plasma prolactin in five patients.[25]

Dana-Haeri and Trimble[7] have found particularly interesting results in the hormonal responses to partial seizures in 22 patients, either with or without clinical psychopathology. Somewhat greater increases in prolactin followed the seizures in the group with psychopathology compared with the group without; LH was occasionally increased, and FSH showed changes in only a few patients. The relationships between temporal lobe discharges and prolactin secretion and psychopathology as well as sexual dysfunction will require further investigation.

ENDOCRINE FUNCTION AND ANTIEPILEPTIC TREATMENT

Anticonvulsant drugs have a number of effects on neuroendocrine functions. These effects have been reviewed by Lühdorf.[19] A particularly

important area is that of oral contraceptives, in that a number of anticonvulsants reduce the efficacy of these agents to about the same level as that of intrauterine devices. Valproic acid reportedly does not have this effect.

Changes in thyroid hormones have been investigated by Bentsen et al.[4] who found that several thyroid parameters were decreased by either carbamazepine or valproic acid, but there were no consistent increases in TSH. The changes could not be easily explained by altered competitive protein binding, but could be due to either decreased hormone synthesis or drug-induced increases in peripheral metabolism of the hormones.

The often-cited stimulating effect of carbamazepine on vasopressin could not be corroborated by Krause.[18] Although several adult epileptics who were taking carbamazepine showed very low levels, this group did not differ significantly from controls or patients taking phenytoin, primidone, or valproic acid. The antidiuretic effect of carbamazepine may be due to increased sensitivity of the kidney to ADH combined with a resetting of osmoreceptors.

Phenytoin and carbamazepine have been shown to increase pituitary responsiveness to LHRH and TRH.[5] LH and prolactin were consistently elevated in response to the releasing hormone, whereas FSH remained unchanged in both male and female patients. The exaggerated LH response suggests that these patients may have primary hypogonadism due to enhanced sex hormone metabolism from induction of hepatic enzymes by the drugs. The effect was not seen in male patients taking carbamazepine, however.

Growth hormone stimulation tests using L-Dopa and prolactin stimulation with metoclopramide were recently reported in epileptics by Franceschi et al.[11] Minor abnormalities of growth hormone secretion were found in patients taking valproic acid, and there were variations in the timing of peak stimulation in patients on phenytoin and multiple drugs. Patients receiving multiple drugs had significantly higher peaks of growth hormones than controls. Significantly higher levels of prolactin were observed in epileptic men taking phenobarbital, phenytoin, and carbamazepine, as well as multiple drugs, whereas valproic acid caused no change in the pattern of prolactin secretion. No abnormalities of prolactin secretion were found in women. No significant differences were found in ACTH or cortisol. Growth hormone responsiveness to oral L-Dopa was unaffected by carbamazepine and phenobarbital, whereas phenytoin, valproic acid, and multiple drug therapy induced differing abnormalities in the latency, amplitude, and duration of growth hormone secretion. These abnormalities of growth hormone may be of little or no clinical importance in adults; however, they may be significant for the fetuses, infants or young children who are exposed to these medications.

SUMMARY

The complex interactions of neurosecretions with the developing brain suggest that it has multiple site and time-specific vulnerabilities that may contribute to the pathogenesis of several forms of epilepsy, yet, on the

other hand, may provide several new forms of therapy. Catamenial seizures can be clearly related to hormonal changes, although other factors are important, such as altered drug metabolism during menses. Progesterone appears to be especially effective in treating seizures. Optimal forms of treatment for catamenial epilepsy have not been established; however, several forms of progesterone are available and may be helpful, including those in oral contraceptives. Special care in the selection of oral contraceptives may be an important adjunct in caring for women with epilepsy.

Altered secretion of neurohormones suggests important clues to the sexual dysfunction and psychopathology associated with temporal lobe epilepsy. New approaches to these patients include the clinical evaluation for sexual dysfunction along with the measurement of prolactin, testosterone, LH, and FSH levels, and treatment of sexual dysfunction by the effective use of anticonvulsants. Elevated plasma hormones (especially prolactin) following seizures can help to distinguish true seizures from pseudoseizures. Effects of anticonvulsant drugs on endocrine function are important, particularly with respect to their ability to lower the efficacy of oral contraceptives by competitive binding. A number of hormonal changes have been described with several drugs, which suggest that their complex central and peripheral effects might help to explain some aspects of normal hormone activity as well as some common side effects of the drugs.

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