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Epilepsy, Sex Hormones, and Antiepileptic Drugs

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Summary: Many factors associated with hormone function have an impact on the course of epilepsy. Patients with epilepsy may have disturbances in sexual function such as anovulatory cycles in women and decreased libido and potency in men. Data indicate seizures, especially those arising in the limbic system, may influence the hypothalamic pituitary axis. Antiepileptic drugs also influence sexual function through direct brain effects as well as through induced changes in pharmacokinetics of the sex steroid hormones. Pregnancy has been reported to be a time of increased seizures; however, this has often been associated with low drug levels, for reasons that include inadequate drug dose, possible changes in pharmacokinetics, and noncompliance. Some evidence suggests that hormones affect seizure frequency. Changes in seizures during the menstrual cycle (catamenial epilepsy) have been found in some women: seizures were fewer during the luteal phase but increased when progesterone levels declined. Some improvement in seizure frequency has been shown in pilot studies using medroxyprogesterone acetate, a synthetic progesterone. Current concepts of the interrelationship among epilepsy, sex hormones, and antiepileptic drugs are discussed. **Key Words:** Epilepsy—Sex hormones—Antiepileptic drugs.

The interactions between epilepsy and sex hormone function are complex. The purpose of this paper is to synthesize what is known about these effects and outline areas where future research in epilepsy and endocrinology is needed (Mattson, 1984). Important issues are (a) what effects do epilepsy and seizures have on the hypothalamic–pituitary–gonadal axis? (b) what effects do female sex steroid hormones have on seizures? and (c) what effects do antiepileptic drugs have on sex hormone physiology?

THE HYPOTHALAMIC–PITUITARY–GONADAL AXIS

The interaction between epilepsy, sex hormones, and antiepileptic drugs is best understood in the context of the normal function of the hypothalamic–pituitary–gonadal axis. The system works in a feedback relationship (Fig. 1). Nuclei in the medial basal hypothalamus can be considered the control center for reproductive sexual physiology (Pfaff and McEwen, 1983). Hypothalamic function is affected by several factors, including hormonal feedback from gonadotropin and gonadal steroid hormones as well as through direct neuronal input from other brain systems (Pfaff and McEwen, 1983). The direct effect of steroid hormones is particularly important in the feedback loop. When circulating sex hormone levels are low, neurons located primarily in the preoptic and mesial basal nuclei of the hypothalamus produce a decapeptide, gonadotropin releasing hormone (GNRH), which travels along the nerve fiber to the area of the median eminence. There, vesicles of the hormone are secreted into the hypothalamic–pituitary portal system and transported to the anterior pituitary gland. GNRH promotes the production and secretion of glycopeptide gonadotropins. In women, the ovary is the primary target organ with special receptive tissue. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) bind to specific membrane receptors and activate adenylate cyclase. This enzyme catalyses production of the second messenger, 3′5′-cyclic adenosine monophosphate, which in turn enhances steroidogenesis and release of estrogen (primarily 17,β-estradiol). In women, FSH increases follicle development with a corresponding peak rise in estrogen. A surge in release of LH and FSH from the pituitary precipitates ovulation. The ruptured

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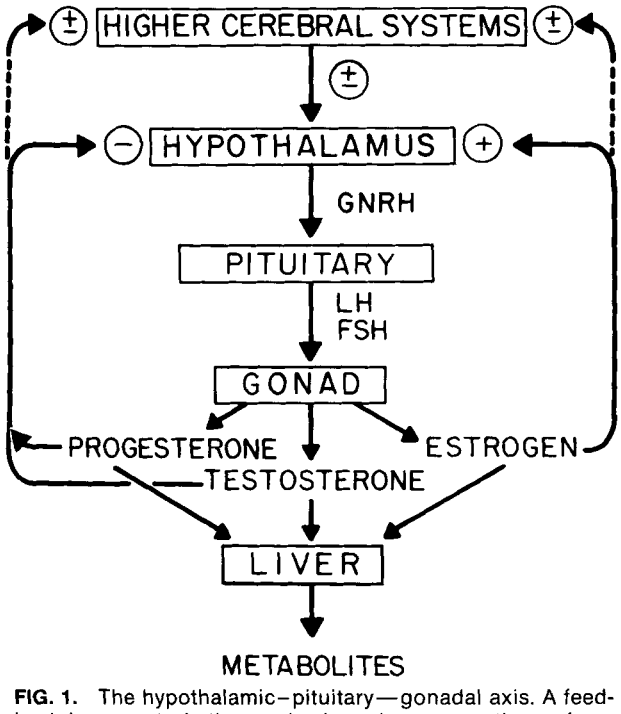

FIG. 1. The hypothalamic–pituitary—gonadal axis. A feedback loop controls the synthesis and concentrations of sex hormones. FSH, follicle stimulating hormone; GNRH, gonadotropin releasing hormone; LH, luteinizing hormone.

follicle undergoes change to form specialized ovarian tissue which produces another rise of estrogen as well as a marked increase in progesterone. The high levels of circulating progesterone inhibit hypothalamic production of GNRH, in turn limiting synthesis and release of LH. In the event that conception occurs, the placenta of the newly inplanted ovum begins to produce chorionic gonadotropin, a peptide similar to LH which maintains the corpus luteum and output of estrogen and progesterone until later in pregnancy when hormone production is assumed by the placenta. In the absence of pregnancy, falling LH results in atresia of the corpus luteum with a subsequent rapid fall in estrogen and progesterone levels. The low hormone levels cause a loss of endometrial lining and the onset of menses. The low levels of estrogen and progesterone also result in a positive feedback to the hypothalamus, a subsequent release of GNRH, and repetition of the cycle (Martin et al., 1977).

The feedback loop in men is much less complex. Low levels of circulating free testosterone result in increased GNRH production and secretion by the hypothalamic nuclei, with subsequent release of LH from the pituitary. LH acts on Leydig cells of the testes to increase production and release of testosterone and dihydrotestosterone (Martin et al., 1977).

The male and female sex steroid hormones are bound to protein for transport in the blood. Anderson (1974) has reviewed the function of sex hormone binding globulin (SHBG) in humans. Of the several possible roles for this binding protein, the most probable include transport of sex steroids in plasma, stabilization of unbound concentration of the sex steroids to facilitate hypothalamic monitoring in the feedback loop, control of metabolism, and clearance and inactivation of sex steroids. Detailed studies by Sodergard et al. (1982) indicate that only 2% of sex steroids circulate in a free, pharmacologically active form. Testosterone is 45% bound to SHBG and 53% to albumin; 17,β-estradiol is 30% bound to SHBG and 68% to albumin. Changes in SHBG concentration produce larger variations in free testosterone than free estradiol because of differences in binding affinity (Anderson, 1974). Progesterone binds to albumin (53%) and corticosteroid-binding globulin (transcortin) (45%).

The sex steroid hormones are distributed to tissues throughout the body and lead to physiological and structural changes. Unlike the glycopeptide gonadotropins, these relatively small steroid molecules are able to cross cell membranes in target cells and bind to specific cytosol plasma receptors. These complexes move to the nucleus and lead to production of messenger ribonucleic acid and subsequent specific protein synthesis. Sex steroid hormones also have specific receptor sites in the hypothalamus which provide access to feedback of these neural transmitters. Progesterone has widespread uptake in the brain (Billiar et al., 1975). The function of sex hormones in other parts of the brain is less well understood; they may be general modulators of brain excitability (Pfaff and McEwen, 1983).

Within this closed loop regulatory system, altered function in one organ affects functioning in other areas of the axis. Reduced function of the hypothalamus or pituitary results in secondary gonadal failure with decreased gonadotropin and sex steroid levels. When gonadal function is diminished, primary gonadal failure occurs with high levels of GNRH, FSH, and LH.

Biotransformation of sex steroid hormones occurs in various tissues, but primary metabolism occurs in the hepatic mixed-function oxidase system with conversion to relatively inactive polar metabolites as well as conjugation to sulfates and glucoronides prior to excretion (Conney, 1967).

EPILEPSY AND SEIZURE EFFECTS ON SEX HORMONE FUNCTION

Virtually all reports of sexual function in patients with epilepsy describe hyposexuality (Gastaut and

Colomb, 1954; Hierons and Saunders, 1966; Blumer and Walker, 1967; Taylor, 1969; Pritchard, 1980; Toone et al., 1980). Gastaut and Colomb (1954) originally concluded that hyposexual function was most frequently seen in patients with temporal lobe epilepsy, and Pritchard (1980) reported similar findings. In more extensive recent studies, Toone et al. (1980) could find no such distinction. Taylor (1969) studied 100 patients who underwent temporal lobectomy for intractable seizures. Approximately two-thirds were considered to have some disturbance of normal sexual adjustment. Hyposexuality resulting from disinterest or lack of libido was the most common finding in both men and women, and was particularly evident when epilepsy developed in childhood. The occurrence of decreased libido and potency more often led to patient complaints about the problem when epilepsy began in adult life. Only one of the 100 patients reported hypersexuality. Ictal changes in sexual behavior occur infrequently in complex partial seizures but are thought to be automatisms mediated through neural structures, rather than an effect on the endocrine system (Spencer et al., 1983). Several authors have found that sexual function improves in some patients following temporal lobectomy if surgery was associated with improved control of the seizures (Hierons and Saunders, 1966; Blumer and Walker, 1967; Taylor, 1969). The role of postoperative medication changes in improved sexual function was not assessed.

Several explanations for hyposexuality in epileptic patients have been proposed. Taylor (1969) believed much of the disturbance in sex function arose as a consequence of seriously compromised social development. Toone et al. (1984) recently studied the frequently reported decrease in libido and potency in men with adult onset seizures. They postulated that these effects may result from an antiepileptic drug-induced alteration in testosterone levels. A possible disturbance of limbic structures in temporal lobe epilepsy has been proposed by other authors (Herzog et al., 1982; Trimble et al., 1984). Wada and Erickson (1962) noted that monkeys undergoing temporal lobectomy subsequently developed irregular menstrual cycles. Extensive interconnections exist between the limbic system and the hypothalamus, through the stria terminalis, fornix, and median forebrain bundle (Sawyer, 1972; Martin et al., 1977). Because seizures commonly arise in the hippocampus and other limbic structures, disease or seizure discharge might well affect neuroendocrinological function as noted in limbic stimulation studies (Popovichenko, 1971; Kawakami and Terasawa, 1972; Ellendorff et al., 1973).

Evidence of specific disturbances of hormonal function in women is minimal. No data indicate that women with epilepsy have any change in fertility. However, Laidlaw (1956) reported a high number of irregular menstrual cycles in his detailed study of catamenial epilepsy. He postulated ovulatory failure but had no data concerning hormone levels. Three recent studies independently reported that an unexpectedly large number of women with epilepsy had anovulatory cycles (Backstrom, 1976; Rosciszewska et al., 1976; Mattson et al., 1981) as indicated by the absence of a luteal phase. None of these studies measured gonadotropins to determine whether the anovulatory cycles were a result of primary or secondary ovarian disturbance of function.

In young men with epilepsy and well controlled seizures, specific study of pituitary function has shown minimal evidence of abnormality. In a detailed investigation, Tartara et al. (1984) tested pituitary hormone and steroid responsiveness before and following pituitary challenge with LHRH and thyrotropin releasing hormone. Normal release of LH, FSH, and prolactin was found. Testosterone levels were in the normal range, but 17,β-estradiol levels were lower and SHBG higher in patients with epilepsy than in controls. Because these patients were receiving antiepileptic drugs, Tartara and coworkers concluded that differences between control values and patients with epilepsy were consistent with drug-induced metabolic changes.

Recent studies provide evidence that seizures induce transient surges of some pituitary hormones. Experimental studies in humans given electroshock or experiencing spontaneous tonic–clonic and partial seizures have shown marked changes in output of pituitary hormones (Ryan et al., 1970; Vigas et al., 1975; Ohman et al., 1976; Trimble, 1978; Pritchard, 1980; Herzog et al., 1982; Aminoff et al., 1984). Some variability in findings appears among the studies, but all note a marked rise of prolactin levels within the first 20 min postictally. Elevation of LH and FSH has been reported less consistently. The pulsatile release of LH produces variable levels. Frequent measurements for an hour may need to be made to find a definite elevation (Tartara et al., 1984; Trimble et al., 1984). The significance of the release of gonadotropins following seizures is conjectural. Persistently high levels of prolactin might be a possible explanation for anovulatory cycles through inhibition of hypothalamic release of LHRH (Clemens et al., 1971). However, the frequency of seizures would need to be high or occur at a specific preovulatory time to have such an effect. Recent studies have demonstrated that the anovulatory effect of elevated prolactin levels in breast feeding is dependent on the frequency of

nursing. Constant modest elevation in prolactin is more effective in inhibiting ovulation than transient high levels.

In summary, clinical and experimental evidence of significant disturbance of the hypothalamic–pituitary–gonadal axis by seizures or brain lesions outside the hypothalamus is incomplete. Data indicate that the axis is relatively independent of significant, long-lasting changes. At the same time, transient surges of gonadotropins accompany seizures, but these surges are of unknown clinical endocrinological significance. It seems that many of the abnormalities of sexual function so commonly associated with epilepsy result from psychological and social factors as well as antiepileptic drug effects. The mechanisms responsible for drug effects remain to be determined (below).

FEMALE SEX HORMONE EFFECTS ON SEIZURE ACTIVITY

Early reports by Gowers (1885) and Locock (1857) suggested that cyclic changes in seizure frequency were related to specific times in the menstrual cycle. Laidlaw (1956) concluded that cyclic variability as in catamenial epilepsy was the result of hormonal effect. Extensive subsequent animal and human studies have supported this hypothesis.

Estrogen

Interactions between hormones and epilepsy in animal experiments have received thorough review (Newmark and Penry, 1980; Timiras and Hill, 1980). Seizure threshold in the hippocampus and amygdala is lowest when estrogen levels are elevated, and reverses when they decline. Administration of estrogen to oophorectomized or hypophysectomized rats has similar effects, suggesting a direct brain action (Wooley and Timiras, 1962*b*). Similar studies in a variety of other animal species and seizure models confirm that estrogens have epileptogenic properties (Wooley and Timiras, 1962*a*,*b*; Werboff et al., 1963; Blackham and Spencer, 1970; Newmark and Penry, 1980). Other studies reported that conjugated estrogens directly applied to cortex elicit seizure activity (Logothetis and Harner, 1960; Marcus et al., 1966). However, Marcus et al. (1966) found that intravenous administration of conjugated estrogens had minimal effect on epileptiform activity unless the blood–brain barrier was impaired and a cortical seizure focus had previously been established.

Clinical evidence that the menstrual cycle can be associated with changes in seizure frequency has been available for more than a century (Gowers, 1885; Locock, 1857). Many clinical studies subsequently noted an association between seizures and menses (Dickerson, 1941; Ansell and Clarke, 1956; Laidlaw, 1956; Logothetis et al., 1959; Sanchez Longo and Gonzalez Saldana, 1966; Livingston, 1972). Logothetis et al. (1959) observed that seizures were exacerbated in a small group of women given estrogen premenstrually in an attempt to treat catamenial epilepsy. In particular, they observed an increase in epileptiform EEG activity in 11 of 16 women given intravenous conjugated estrogens. This observation led to extensive animal and human studies of the epileptogenic properties of estrogen. An increase in seizure frequency in the follicular phase when estrogen levels are highest was found by Backstrom et al. (1976) and Helmchen et al. (1964). In addition, seizure frequency increased during anovulatory cycles, especially at the time of peak estrogen levels. Studies in our clinic confirmed increased seizure frequency during anovulatory cycles (Mattson et al., 1981).

Progesterone

Over forty years ago, Selye (1942) demonstrated that progesterone protected against pentylenetetrazol-induced seizures. Since that time other studies have confirmed that some steroids (progesterone, desoxycorticosterone) elevate electroshock thresholds in animals (Spiegel and Wycis, 1945; Woodbury, 1983). Craig (1966) tested a large number of steroids including a variety of progestins and found that many had anticonvulsant effects independent of hormonal potency. Various other studies of progesterone, medroxyprogesterone acetate (MPA), and lynestrinol in the past three decades have confirmed some decrease in seizure susceptibility in animal models tested for electroshock threshold, pentylenetetrazol threshold, audiogenic seizures, kindling, and focal cortical spikes (Selye, 1942; Speigel and Wycis, 1945; Costa and Bonnycastle, 1952; Wooley and Timiras, 1962*a*,*b*; Werboff et al., 1963; Craig, 1966; Blackham and Spencer, 1970; Langren et al., 1978; Holmes et al., 1984). The antiepileptic properties of various progestins are quite different. For example, Holmes et al. (1984) demonstrated that progesterone was less effective in inhibiting development of kindling in rats than a derivative (alphadione) devoid of endocrine function. Backstrom et al. (1984*a*) and Craig (1966) also reported that antiepileptic efficacy is not related to hormone potency in animal and human studies.

In the study of seizure frequency and menstrual cycles, Laidlaw (1956) described a consistent decrease in seizures near the mid-luteal phase. He hypothesized that high progesterone levels at this time prevented seizures, whereas rapid fall at and immediately prior to menses facilitated attacks. Backstrom (1976) also demonstrated a decreased number of seizures in women during the luteal phase and confirmed that this correlated with the highest concentration of progesterone. An increased number of seizures was seen in the follicular phase when estrogen levels increased. He concluded that seizure susceptibility correlated best with the estrogen/progesterone ratio.

Hall (1977) successfully treated a patient who suffered from catamenial epilepsy with norethisterone, a synthetic progestin. Subsequently, Zimmerman et al. (1973) used depot administration of MPA to treat a young woman with intractable seizures. Our preliminary study of MPA therapy in 16 women revealed a statistically significant reduction in seizure frequency for some who had been refractory to standard drug therapy (Mattson et al., 1984*a*,*b*). A controlled trial by Dana-Haeri and Richens (1983) failed to show any difference in seizure frequency in women receiving norethisterone compared to a placebo-treated group. The lack of evidence of antiepileptic effect may have been caused in part by the fact that norethisterone is a testosterone-derived synthetic steroid rather than a hydroxyprogesterone, and has weaker effects. Furthermore, cyclic rather than continuous administration of the oral contraceptive might fail to inhibit cyclic release of FSH and a secondary rise in estrogen levels. Studies by Backstrom et al. (1984*b*) and Landgren et al. (1978) indicate that progesterone infusion in women with epilepsy results in suppression of epileptiform spikes in some but not all patients. The dose of progesterone administered produced blood levels comparable to those found during the luteal phase of the menstrual cycle.

The mechanism of action of sex hormones on seizure activity is unknown. In experimental and human studies, intravenous administration of conjugated estrogens increases epileptiform activity in as little as 30 s (Logothetis et al., 1959). Similarly, intravenous progesterone suppresses spikes in women with epilepsy in a comparably short period (Backstrom et al., 1984*b*). Such a rapid effect is not characteristic of the mechanisms by which sex steroid hormones typically elicit cellular effects (Pfaff and McEwen, 1983). The usual stimulation and formation of new protein is a slower process, requiring at least 10–15 min and more often hours or even days (Anderson et al., 1975; Pfaff and McEwen, 1983). The rapid onset of action in these experimental models suggests a direct effect on neural membranes (Pfaff and McEwen, 1983). Such action, not directly related to the sex hormone reproductive tissue activity of these compounds, is consistent with the observation that some analogs or metabolites of progesterone have more potent antiepileptic effects than the steroid hormone most active in producing sexual effects (Craig, 1966; Holmes et al., 1984). Such a mechanism does not preclude an indirect, hormonally mediated action. In our study (Mattson et al., 1984*a*,*b*) of women treated with MPA, a synthetic progestin having relatively weak antiepileptic properties (Meyerson, 1967), improved seizure control correlated best with development of amenorrhea after administration of parenteral MPA (Mattson et al., 1985) rather than with the blood level of MPA. Feedback inhibition of gonadotropin synthesis and release may have minimized seizures by preventing the cyclic peak in estrogen levels. Other factors that could contribute to changes in seizure frequency during the menstrual cycle might be indirect sex hormone influences through changes in water retention (Ansell and Clarke, 1956), drug pharmacokinetics (Fernandez-Pol and Zaninovich, 1975; Shavit et al., 1984) or behavioral state (Bandler et al., 1957).

In summary, sufficient evidence from animal and clinical studies confirms the effects of female sex steroid hormones on brain and seizure excitability. Estrogen compounds lower seizure threshold and increase seizure frequency. Progestins have an opposite effect. Analogues and metabolites of the sex hormones differ considerably in their effect on electrical discharges without respect to hormone potency (Craig, 1966; Backstrom et al., 1984*a*,*b*; Holmes et al., 1984). Further search for progestins possessing antiepileptic properties but without hormonal effect is warranted.

Pregnancy effects

Most reports indicate some increase in seizure frequency or severity during pregnancy (Suter and Klingman, 1957; Knight and Rhind, 1975; Mygind et al., 1976; Dam and Dam, 1980; Schmidt, 1982). In 1907, Turner reported the results of studying 61 pregnancies in 41 women. He found an increase in 23 instances, improvement in 6, and no change in 32 pregnancies. However, some increase in seizure frequency was reported during labor or the postpartum period in another 22 women. Schmidt (1982) recently reviewed the previous literature reporting on 2,165 pregnancies and found that seizure fre-

quency increased in 522 (24%), decreased in 492 (23%), and remained unchanged in 1,151 (53%). Retrospective analysis did not allow discrimination among the types of patients or epilepsy most likely to be associated with worsening or improvement. Most recently, in prospective studies, Schmidt et al. (1984) reported that in a group of 136 pregnancies, seizures increased in 50 (37%), decreased in 18 (13%), and did not change in 68 (50%). Increase in seizure frequency and severity was usually related to decreasing anticonvulsant blood levels. Sleep deprivation was the most important factor precipitating seizures among 23 pregnancies in women who were not receiving antiepileptic drugs. Battino et al. (1984) studied 74 pregnant women and performed extensive clinical and endocrinological studies prospectively. They reported results comparable to those of Schmidt et al. (1984), with some increase of seizures in 21 women, decreased seizures in 12, and no change in 41. They observed a statistically significant positive correlation between increased seizure frequency and high urinary estrogen secretion. Ramsey et al. (1984), in a separate series, could find no correlation of seizures with rising estrogen levels. They concluded that although estrogen levels rose in pregnancy, a concomitant increase in progesterone caused a relatively constant estrogen/progesterone ratio. In addition, a maximal peak rise in estrogens toward the end of pregnancy was caused by increased levels of estriol rather than 17,β-estradiol. Estriol has relatively weak physiological action relative to estrone or 17,β-estradiol (Martin et al., 1977).

Schmidt et al. (1984) found that a decrease in antiepileptic drug levels most often explained seizure exacerbation, and attributed this to noncompliance. Changes also have been found in the pharmacokinetics of antiepileptic drugs leading to lower blood levels (Ruprah et al., 1980). Nau et al. (1984) reported decreased phenytoin levels associated with evidence of increased drug clearance. This was presumed to be the result of enhancement of hepatic monooxidase enzyme systems. Increase in drug clearance was confirmed by Ramsay et al. (1984). Philbert et al. (1984) attributed the decrease in phenytoin levels to changes in binding and volume of distribution rather than to changes in clearance. Similarly, increased clearance of primidone caused lowering of primidone levels without concomitant increase in the derived metabolites, PEMA and phenobarbital (Kaneko et al., 1984). Extensive evidence is available to indicate that a modest increase in seizure frequency may be observed during pregnancy, although the majority of women experience no change. Careful regulation of dose and blood levels throughout pregnancy, coupled with good compliance and avoidance of precipitating factors, makes it likely that women with epilepsy should have no more difficulty with seizures during pregnancy than at other times.

ANTIEPILEPTIC DRUG EFFECTS

Antiepileptic drugs have unwanted effects on sex function. Indeed, the introduction of bromides in the treatment of epilepsy was based on the observation that these salts produced impotence (Locock, 1857), as epilepsy was believed by some to be related to excessive sexuality. Considerably evidence now exists to suggest that antiepileptic drugs change the metabolism of hormones with alteration of circulating blood levels and secondary effects on the feedback loop of the hypothalamic–pituitary–gonadal axis. Much less information is available concerning direct effects of antiepileptic drugs on the function of the hypothalamus and other brain areas influencing sexual behavior and physiology.

Metabolic changes

An association between drugs and hormones may be a consequence of the fact that both types of compounds are hydroxylated by a common hepatic microsomal enzyme system (Conney, 1967). Thus, drug therapy can alter the hydroxylation of steroid hormones, and hormone treatment can affect the metabolism of drugs. Conney et al. (1966) demonstrated that phenobarbital can alter the binding, transport, or physiological disposition of steroids. They demonstrated increased in vitro hydroxylation of progesterone and other steroids by liver microsomes, and postulated that drugs known to be microsomal enzyme stimulators, e.g., phenobarbital, can alter the actions of endogenous steroids or exogenous steroids administered therapeutically. Both phenytoin and phenobarbital have long been known to be potent stimulators of hepatic microsomal enzyme activity in animals (Conney, 1967). Carbamazepine induces its own metabolism as well as that of other drugs. There is clinical evidence indicating that the use of antiepileptic drugs affects hormones, suggesting drug-induced alterations in hypothalamic–pituitary–gonadal function (Richens, 1984).

Oral contraceptives and antiepileptic drugs

In 1974, Janz and Schmidt reported the failure of oral contraceptive pills in three of their patients receiving antiepileptic drugs. Since that time, other reports have confirmed this observation (Schmidt, 1981). Coulam and Annegers (1979) found a significant increase in the rate of oral contraceptive fail-

ures in a large sample of women also taking antiepileptic drugs. The interaction between antiepileptic drugs and oral contraceptives was evaluated by Back et al. (1980*a*,*b*), who found decreased ethinylestradiol levels with no change in FSH, progesterone, norethindrone, or norgestrel. Interestingly, elevated SHBG concentration was noted in these patients. Back and co-workers suggested use of a high-dose oral contraceptive when breakthrough bleeding occurs for patients taking antiepileptic drugs. They later postulated that antiepileptic drugs, which are enzyme-inducing agents, stimulated production of SHBG. Steroid components of oral contraceptives bind to SHBG at a higher than expected level, thereby decreasing circulating free synthetic steroids (Backstrom and Sodergard, 1977). Other animal studies have demonstrated that phenobarbital increases the first-pass effect for orally administered norethisterone (Back et al., 1980*a*,*b*). Oral contraceptives are particularly susceptible to increases in first-pass effect and changes in gastrointestinal absorption, which could reduce circulating hormone concentration (Breckenridge et al., 1979). This is not the case with intramuscularly injected hormones. Risk of failure with low-dose oral contraceptives suggests use of alternate formulations for women using antiepileptic drugs such as those containing higher hormone concentrations (Orme, 1982).

Induction of synthetic progesterone metabolism has also been demonstrated in animals (Saarni et al., 1983) and humans (Mattson et al., 1984*a*,*b*). Medroxyprogesterone levels were 30–70% lower in women receiving antiepileptic drugs than in controls receiving comparable doses of oral or parenteral MPA (Mattson et al., 1984*a*,*b*). Rats pretreated with phenobarbital not only had faster clearance of MPA but also had enhanced elimination of polar metabolites (Saarni et al., 1983). Because of increased clearance and binding of SHBG, the biological effectiveness of both endogenous sex steroids and exogenous synthetic sex steroids can be reduced. Thus, use of oral contraceptives by women taking antiepileptic drugs often results in breakthrough bleeding, which indicates a risk of pregnancy (Orme, 1982).

No change in seizure frequency has been found in women using oral contraceptives. Although an early report (Bickerstaff, 1975) suggested aggravation of seizures, this has not been confirmed. A study by Toivakka (1967), followed by placebo-controlled trials of oral contraceptives (Espir et al., 1969; Dana-Haeri and Richens, 1983), confirmed that use of pills containing estrogen and progesterone does not cause an exacerbation of seizures for women whose epilepsy is not well controlled.

Antiepileptic drugs and sex hormone binding globulin

Victor et al. (1977) first noticed that women taking antiepileptic drugs have higher than normal SHBG levels. They suggested that free sex hormone levels are lowered by the induced increase in SHBG, resulting in altered steroid action. Barragry et al. (1978) also demonstrated elevated SHBG levels in men and women, with increased total testosterone concentration in males using antiepileptic drugs. They postulated that antiepileptic drugs selectively induce hepatic SHBG synthesis without affecting other transport proteins associated with thyroxine, cortisol, or vitamin D binding globulin.

Toone et al. (1980) suggested that antiepileptic drug therapy increases SHBG, leading to decreased free testosterone and thereby affecting the hypothalamic–pituitary–gonadal axis. They noted decreased libido in treated patients. Again, the association was made that antiepileptic drugs enhanced sex hormone metabolism. This concept is supported by the findings of Dana-Haeri and Richens (1981) that patients receiving multiple antiepileptic drugs had higher LH levels than patients on sole drug, suggesting dose-related induction. In this case, low free hormone levels would serve to activate LH release. Tartara et al. (1984) found hormone changes in well-controlled epilepsy patients only in those receiving antiepileptic drugs. Levels of 17,β-estradiol were decreased and SHBG was increased.

Drug effects on male sexual function

Several clinical studies support the concept that hypothalamic function and steroid metabolism are affected by drugs. Alcoholics and marijuana and heroin users have decreased testosterone, probably because of the previously described metabolic induction caused by these drugs.

Recently, attention has been redirected to reports that, especially in male epileptics, sex drive often is diminished, and that antiepileptic drugs may play an important role. The Veterans Administration Cooperative Study of Antiepileptic Drugs has preliminary evidence that decreased potency and libido are important side effects of antiepileptic drug treatment. The incidence of occasional or continued impotence reached 12% in patients beginning therapy with a single drug, which usually could be reversed by changing medication (Mattson et al., 1985). Toone et al. (1984) reported reduced sex activity in a group of 27 male patients; they did not find a

decrease in total testosterone levels, but linked decreased function to lowered free levels. Dana-Haeri and Richens (1981) also suggested that free testosterone might be decreased because of antiepileptic drug effects on hormone binding. Christiansen and Lund (1975), investigating androgen metabolism and sexual potency in male patients treated with antiepileptic drugs, found a significant increase in impotence among men receiving multiple drugs, and low volume and motility in sperm samples. Excretion of androsterone, the main androgenic metabolite, was inversely correlated to impotence. These authors hypothesized that antiepileptic drugs increased the metabolism of steroid hormones, but they did not complete an evaluation of the hypothalamic–pituitary axis.

The enzyme-inducing properties of antiepileptic drugs enhance metabolism and clearance of free testosterone, while an increase in SHBG results in increased testosterone binding and less circulating free drug (Anderson, 1974). However, the testosterone levels are still within normal range. Although modest changes in testosterone levels are poorly correlated with potency, Daniels et al. (1984) had some success in reversing drug-related impotence with testosterone therapy.

Direct antiepileptic drug effects

The concept of an interaction between drugs and steroid hormones is insufficient to explain sexual disturbances. Antiepileptic drugs may also influence the hypothalamic–pituitary–gonadal axis directly, because change to another drug or discontinuation of treatment often corrects the problem (Mattson et al., 1985). Decreased libido and potency were more commonly reported with use of phenobarbital or primidone than with phenytoin or carbamazepine, despite the fact that all four drugs are potent enzyme inducers (Mattson et al., 1985). Animal experiments also demonstrate that phenytoin may block ovulation in rats (Quinn, 1965).

CONCLUSION

Understanding of reproductive system function in animals and humans has expanded at a rapid rate. On the other hand, knowledge of the effects of disturbances of brain function, including seizures, on the sexual/endocrine system remains limited, both in humans and animals.

An understanding of seizure occurrence during pregnancy has been advanced despite inconsistencies in data on pharmacokinetic changes of antiepileptic drugs in pregnant women. The evidence seems clear at this time that hormonally induced changes in drug pharmacokinetics play a comparatively small role in seizure occurrence. More extensive, large-scale studies are required to assess women with various seizure types throughout their pregnancies. Frequent measurement of blood levels of antiepileptic drugs and appropriate monitoring of hormone levels and gonadotropins are needed in order to determine whether there is a specific group of women in whom a cyclic pattern can be identified. Certainly, animal studies provide persuasive evidence that pharmacologic doses of estrogens are epileptogenic. It is less clear whether significant effects are detectable with physiological levels of other hormones. Information concerning the possible antiepileptic effects of progestins is much less clear. Animal studies in general show a modest effect of pharmacologic doses of the hormone. However, the type of progestin greatly alters anticonvulsant potential. Some analogs lacking specific hormone properties have shown greater than usual antiepileptic effect. If metabolites with antiseizure efficacy become available and are demonstrated to be relatively safe and nontoxic, then further studies in animals and subsequently in women offer an avenue for development of new treatment strategies which deserve further investigation.

The effects of antiepileptic drugs on sex hormones have been well studied: enzyme induction shortens hormone half-life, increases levels of SHBG, and secondarily lowers free hormone levels, resulting in modest elevation of gonadotropins. Whether these changes have clinical significance in altering normal menstrual cycling, fertility, or male libido and potency remains unresolved. Drugs are clearly significant in affecting the elimination of synthetic contraceptive hormones, leading to a higher than usual failure rate. Alternative methods of birth control or antiepileptic drug therapy may resolve these problems on a practical level.

Antiepileptic drugs may affect sexual behavior by acting on the reproductive system via direct effects on the brain, specifically the hypothalamus, as well as via the hypothalamic–pituitary–gonadal axis. Little work has been done in this important area. The potential for observational as well as neuroendocrine studies in primates with experimental or spontaneous seizures offers an area of investigation of great interest and clinical importance.

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Discussion

Dr. Pedley: Dr. Mattson, do anticonvulsants affect the levels of growth hormone or other hormones, in addition to the sex hormones you discussed in your talk?

Dr. Mattson: There seems to be considerably less effect on other hormones. Trimble found an immediate release of antidiuretic hormone that would be missed on most studies because it occurs immediately after the seizure.

Dr. Pedley: Another question for you, Dr. Mattson, relates to treatment. Should women on antiepileptic drugs be advised not to use very low estrogen–progesterone contraceptives, and do you make recommendations to them or to their gynecologists regarding this issue?

Dr. Mattson: That is difficult to answer. There is an increased risk of conception in that circumstance, about to the risk seen with other effective forms of contraception. At least one author believes that breakthrough bleeding is evidence that the pill is not working and that since protection against conception cannot be assumed, some other form of contraception should be used under these circumstances.

Another choice, of course, is to use a higher-dose estrogen tablet, but I do not think anyone knows if this is a solution to the problem. While this might improve contraceptive effects, it could conceivably increase other risks of hormonal contraception.

Dr. Pedley: Dr. Mattson, would you consider the use of progestin agents in a woman with intractable seizures if her seizure diary demonstrated a relationship to the menstrual cycle?

Dr. Mattson: I think that use of these compounds at this time is premature, and I believe their use is still investigational. In our research experience, at least half of the women we treated this way had undesirable spotting or bleeding. This may be because they are clearing the hormone too rapidly for an optimal effect. Nonetheless, for many reasons, not all of them medical, use of Provera for clinical purposes is not warranted at this time except in an investigative setting. As you know, the Food and Drug Administration recently reviewed allowing Depo-Provera to be used as a contraceptive drug and, again, turned it down.

Dr. Pedley: Dr. Mattson, is there a decrease in the fertility of epileptics that is independent of libido?

Dr. Mattson: I don't know. I am not aware of any carefully controlled studies that indicate women with epilepsy are less fertile. There have been some studies that indicate that spermatogenesis is reduced or abnormal in males taking antiepileptic drugs but, again, I do not know if there is any clinically significant inability of potent males to effect conception.

Dr. Pedley: Dr. Mattson, would you explain why you stated that decreased testosterone levels were not responsible for hyposexuality in male epileptics, since Toole's study showed that, with withdrawal of medications and increasing testosterone levels, normal sex function was restored?

Dr. Mattson: Return of normal sexual function following drug withdrawal does not mean that this is related to sex hormones. There is no doubt that antiepileptic drug use is associated with decreased libido and potency but other factors are probably as important as decreased testosterone. I am not persuaded that the evidence shows this is solely, or

mainly, related to testosterone metabolism. We have found that the incidence of decreased libido and impotence is considerably different among the various antiepileptic drugs, all of which are potent enzyme inducers and would be expected to have comparable effects on testosterone. Indeed, we have studied free and total testosterone levels in a group of patients on monotherapy, some of whom developed sex problems. There were no significant differences between those with and without sexual dysfunction. Sex hormone binding globulin was also not a significant variable.

So I think that while the observations on testosterone are interesting, most endocrinologists feel that the measured changes are of trivial significance compared to other factors that affect normal libido and potency.