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Editorial Commentary

Hormonal Changes in Epilepsy

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Hormonal changes, especially low levels of biologically active testosterone (T), may contribute to diminished potency and hyposexuality in men with epilepsy (1–6). Two possible mechanisms are advanced in this issue of *Epilepsia*.

Testosterone exists in the serum in three forms: free (2–3%), albumin-bound (53–55%), and sex hormone-binding globulin (SHBG)-bound (43–45%). Free testosterone and the large pool of testosterone that is loosely bound to albumin are available to tissues. They constitute T. The SHBG-bound fraction is not biologically active. Several antiseizure drugs induce hepatic synthesis of increased amounts of SHBG. This can result in normal or even elevated levels of total testosterone, while the concentration of T is reduced, as measured by non SHBG-bound testosterone or estimated by free testosterone or free androgen index (7).

In this issue, Isojärvi et al. (8) present data to suggest that SHBG levels increase progressively over time during chronic treatment with carbamazepine (CBZ) and phenytoin (PHT). This may explain a concomitant decrease in T. Correspondingly, none of their subjects had sexual dysfunction during the first 5 years of therapy, while diminished potency existed in two of three subjects who had been treated for >20 years.

A possible role for estrogen is raised by Murialdo et al. (9). Estradiol levels are significantly higher in men with epilepsy treated with PHT than in either untreated epileptic men or normal controls (10). It is likely that this is a direct effect of antiseizure drugs because the serum concentration of biologically active estradiol correlates with serum PHT levels (11). Hepatic dysfunction, however, is not likely to be a mechanism (11). This raises the possibility, therefore, that some antiseizure drugs lower T not only by inducing SHBG synthesis, but also by inducing aromatase, which converts free testosterone to estradiol. Although estradiol constitutes only 1% of male gonadal steroids, it exerts almost 50% of the negative feedback on male luteinizing hormone (LH) secretion (12,13). Suppression of LH secretion results in hypogonadotropic hypogonadism (HH). Chronically low T may lead to testicular failure and hypergonadotropic hypogonadism. This may explain the increased occurrence of both of these reproductive endocrine disorders in men with epilepsy (4). Finally, estradiol produces premature aging of the hypothalamic arcuate nucleus (14,15), another possible cause of HH and, conceivably, the premature decline of testosterone levels (16).

In this issue, Murialdo et al. (9) report significantly higher serum estradiol levels and significantly lower ratios of free testosterone to estradiol in hyposexual men with epilepsy than in either sexually normal men with epilepsy or normal controls. They find, moreover, that the LH response to stimulation by gonadotropin-releasing hormone is blunted in hyposexual men, a finding consistent with HH. Our own observation of an inverse correlation between estradiol/testosterone ratios and LH pulse frequency in PHT-treated men with epilepsy provides further support for a role of estradiol in the development of HH (Fig. 1).

These two newly proposed mechanisms for hyposexuality may, in fact, be related. Antiseizure drugs can induce elevations in estradiol (10). Estradiol stimulates SHBG synthesis while testosterone inhibits it (17). Increased estradiol then results in decreased T. The decrease in T/estradiol ratio stimulates additional SHBG synthesis. This sequence could lead, over time, to a progressively increasing concentration of SHBG and a progressively decreasing T level.

Testosterone increases potency and libido (18,19), while estradiol lowers male sexual interest

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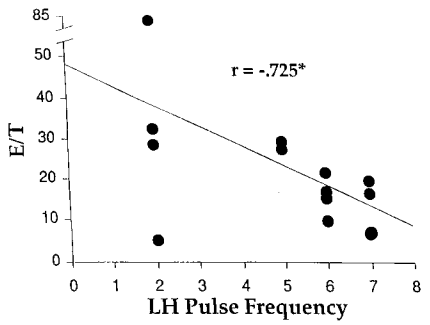

FIG. 1. Relationship of the ratio of non-sex hormone-binding globulin-bound portions of serum estradiol (E)/ biologically active testosterone (T), to 8-h luteinizing hormone pulse frequency (LHPF). Asterisk indicates significance at $p < 0.01$ level by Spearman's rank order correlation coefficient test.

and function (20). It is conceivable then that some antiseizure drugs may act over time to produce a critically low ratio of T/estradiol, sufficient to become clinically manifest as hyposexuality and reduced potency.

Estradiol considerations could be important in treatment as well (10). In our experience, testosterone therapy has been only moderately effective in restoring reproductive and sexual function (21). Moreover, testosterone has not reduced seizure frequency despite some reports of anticonvulsant properties in experimental animals (22). One possible explanation is that antiseizure drugs that induce increased enzyme synthesis may enhance the conversion of testosterone to estradiol by aromatase (23). Because estradiol increases seizure discharges (24,25) and lowers male sexual interest and function (20), higher estradiol levels induced by antiseizure drugs could antagonize the potential beneficial effects of raising testosterone levels. In support of this possibility is a case report in which addition of testolactone, an aromatase inhibitor, and testosterone to baseline CBZ therapy improved sexual questionnaire scores and decreased seizure frequency more than the addition of testosterone alone in a man with intractable seizures and hyposexuality (26).

Reproductive endocrine disorders are also common in women with epilepsy, especially polycystic ovarian syndrome and hypothalamic amenorrhea (27,28). Reproductive endocrine disorders are characterized by anovulatory cycles. Anovulatory cycles are clinically relevant to both epilepsy and reproductive function. They are associated with higher seizure frequency (29,30) and cause menstrual disorders, infertility, and, possibly, in the case of hypothalamic amenorrhea, hyposexuality (27).

In this issue, Cummings et al. (31) report that a remarkable 35.3% of women with partial seizures arising from the temporal lobe (TLE) had anovulatory cycles over an observation period of three consecutive menstrual cycles, compared to 8.3% of normal controls ($p < 0.005$). Anovulatory cycles were not related to seizure frequency, but were more common in women with TLE than in women with primary generalized epilepsy (PGE) ($p < 0.03$). They were also possibly more frequent with polytherapy than monotherapy ($p < 0.12$).

TLE may disrupt the normal limbic modulation of hypothalamopituitary secretion and promote the development of reproductive endocrine disorders (23,27). The laterality and location of epileptiform discharges may determine the development of specific reproductive endocrine disorders (32,33). The findings of Cummings et al. (31) suggest that TLE may have a greater effect on reproductive function than PGE. On the other hand, reproductive endocrine disorders are also common in PGE (28,34). The generalized seizures of PGE, after all, also involve the temporal lobe and limbic structures, although ictal and interictal activity differ considerably between PGE and TLE.

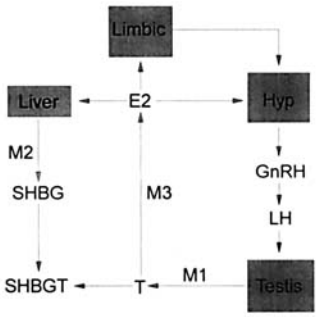

FIG. 2. The hypothalamopituitary axis (Hyp) regulates testosterone secretion by the testes. Hypothalamic gonadotropin-releasing hormone (GnRH) is secreted in a circhoral pulsatile fashion mainly by the arcuate nucleus. It stimulates pituitary luteinizing hormone (LH) release to reflect GnRH pulse parameters. Temporolimbic epileptiform discharges can alter LH secretion. In particular, they produce a significantly wider than normal range of mean baseline and pulse frequency of LH secretion (5). The nature, specific location, and laterality of limbic discharges may be important determinants of specific patterns of LH secretion (5). Some antiepileptic drugs inhibit testosterone synthesis by the testes (M1) (40). They can also act on the liver to increase synthesis of sex hormone-binding globulin (SHBG) (M2), thereby lessening the biologically active portion of testosterone (T) (8). They may also increase the conversion of testosterone to estradiol (E2) by aromatase (M3) (10), which would also lower T. Because E2 stimulates, and androgens suppress SHBG synthesis, the net result may be a progressive increase in E2 / T and a premature decline in serum T levels. Increased E2 / T may play a role in sexual dysfunction (9). Medication-induced elevations in E2 may act through the limbic system to induce epileptiform discharges, and at the hypothalamic level decrease GnRH secretion, produce HH, and cause premature aging of the arcuate nucleus, which may also contribute to HH and early decline in reproductive function.

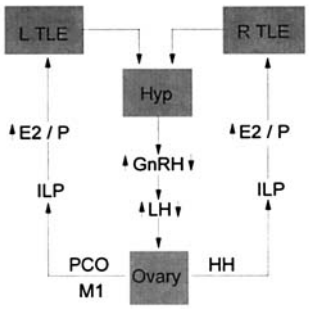

FIG. 3. The ovary secretes estrogen and progesterone under the regulation of pituitary gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone. Gonadotropin levels are controlled by the pattern of hypothalamic (Hyp) gonadotropin-releasing hormone (GnRH) secretion. The mean baseline and pulse frequency of LH secretion may be determined by the nature, specific location, and laterality of temporolimbic electrical discharges. Specifically, left temporolimbic epilepsy (L TLE) is associated with increased mean baseline and frequency of pulses (33), and the development of polycystic ovarian syndrome (PCO) (32). Right temporolimbic epilepsy (R TLE) is associated with low baseline and frequency of pulses (33), and the development of hypothalamic amenorrhea (hypogonadotropic hypogonadism, HH) (32). In women with nontemporal epileptiform discharges, it may be right-sided laterality that is associated with the development of PCO (32). Both of these reproductive disorders are characterized by anovulatory cycles with inadequate luteal phase (ILP) (27), and ILP cycles are unusually common in women with TLE (31). The resulting elevation in estradiol to progesterone ratio may exacerbate seizure frequency (29). Some antiepileptic drugs may differ in their association with the development of reproductive and endocrine disorders. Specifically, chronic valproate (VPA) therapy has a strong association with PCO (M1) (41). This may reflect a specific mechanism by which VPA either induces the development of PCO or the difference between the effects of VPA and hepatic enzyme-inducing drugs on the metabolism of testosterone in epilepsy-associated PCO.

The role of drug treatment cannot be dismissed. In the study of Cummings et al. (31), for example, valproate use was more common among subjects with PGE than TLE, and the effects of polytherapy versus monotherapy need to be assessed using larger numbers of subjects to reach a meaningful conclusion.

The high frequency of anovulatory cycles among women with TLE requires consideration of the role of hormonal therapy (35). Anovulatory cycles are characterized by high estradiol/progesterone ratios. Estrogen is generally epileptogenic, while progesterone has anticonvulsant properties (35,36). Seizure frequency is related to estradiol/progesterone ratios, and seizures are more common in anovulatory cycles (29,30). Treatment with natural progesterone, therefore, may be beneficial (37,38). In an open trial for 25 women with intractable complex partial seizures of temporal lobe origin and catamenial patterns of exacerbation, progesterone reduced both complex partial and secondarily generalized seizures by >50% during three treatment cycles compared to three baseline cycles (39).

Conceptual neuroendocrine models of the interactions among hormones, antiepileptic drugs, and the brain in men and women with epilepsy are presented in Figs. 2 and 3.

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