Available online at www.sciencedirect.com
SCIENCE DIRECT®
Epilepsy & Behavior 7 (2005) S22–S28
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Human sexuality, sex hormones, and epilepsy

George L. Morris III [a,*], Colleen Vanderkolk [b]

[a] *Regional Epilepsy Center, St. Luke's Medical Center, Milwaukee, WI, USA*
[b] *Medical College of Wisconsin, Milwaukee, WI, USA*

Received 24 August 2005; accepted 24 August 2005
Available online 20 October 2005

Abstract

The function of the hypothalamic–pituitary axis (HPA), including the production of luteinizing hormone, follicle-stimulating hormone, gonadotropin-releasing hormone, and prolactin, and the concentrations and metabolism of its end products, such as estrogen, testosterone, and dehydroepiandrosterone, appear to be modified in many people with epilepsy. Effects of the disorder itself and effects of antiepileptic drugs (AEDs) both appear to contribute to these hormonal alterations, which may be associated with sexual dysfunction. Focal epileptic discharges from the temporal lobe may affect HPA function, as is suggested by the normalization of androgen levels seen in men with temporal lobe epilepsy who become seizure-free after surgery. Hepatic enzyme-inducing AEDs such as carbamazepine and phenytoin may be most clearly linked to altered metabolism of sex steroid hormones, but valproic acid, an enzyme inhibitor, has also been implicated in the causation of reproductive endocrine abnormalities. Polycystic ovaries and polycystic ovarian syndrome (PCOS) are widely believed to be common in women with epilepsy, but the actual prevalence and the pathogenesis of PCOS in this population are disputed. Hormonal changes and sexual dysfunction need to be addressed in any comprehensive approach to epilepsy management, as well as any comprehensive epilepsy research program. Avoidance of enzyme-inducing AEDs and achievement of freedom from seizures as the goal of treatment are strongly recommended.

Keywords: Hypothalamic–pituitary axis; Sex hormones; Luteinizing hormone; Follicle-stimulating hormone; Prolactin; Testosterone; Estrogen; Temporal lobe epilepsy; Antiepileptic drugs

1. Introduction

Endocrinologic changes associated with epilepsy can reasonably be expected, in view of the complex and close interconnections between the hypothalamic–pituitary axis (HPA) and the limbic system. Outputs to the HPA from the limbic cortex, including nuclear structures within the amygdala, modify key factors in the release of sex hormones. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) regulate many aspects of gonadal function in both men and women; their secretion by cells in the anterior pituitary is regulated by the release of gonadotropin-releasing hormone (GnRH) from cells in the hypothalamus, while GnRH release is subject to feedback control by gonadal hormones including estrogen and testosterone.

The products of the HPA, including estrogen, testosterone, and dehydroepiandrosterone (DHEAS), have significant effects on sexual end organs. The concentrations of these hormones and their effect on end organs can be influenced by LH, FSH, and prolactin (PRL), and their metabolism can be influenced by a broad variety of factors. The factors that affect the HPA include epileptic activity and medication effects; the latter are the subject of a larger, but skewed, research literature. This article reviews those factors and the ways in which they may be modified in people with epilepsy.

2. Sexual function, sexual dysfunction, and hormonal factors

One of the challenges of defining sexual dysfunction is the need to define normal function. Frequently cited

* Corresponding author. Fax: +1 414 385 8781.
E-mail address: george.morris@aurora.org (G.L. Morris III).

1525-5050/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2005.08.028

reports, including *The Ganus Report on Sexual Behavior*, revealed that two-thirds of men and women reported weekly sexual activity [1]. Nevertheless, the criterion of normal function is clearly open to interpretation, and an objective measure is needed in clinical research. In well-controlled studies that consider sexual function and dysfunction, a standardized instrument such as the commonly used Bear–Fedio Personality Inventory, which assesses a number of traits including sexual interest, is administered to epilepsy patients and healthy sex- and age-matched controls. The use of the standardized inventory and the comparison with a control group together provide an objective criterion of ''normal'' or unimpaired sexual function. The use of a control group may also serve to adjust for cultural variability related to geographic and chronologic differences.

Fenwick et al. [2], in a study of 10 men with epilepsy, showed that 5 of the patients had low levels of total and free testosterone and that these 5 had diminished sexual activity and reduced nocturnal penile tumescence. Circulating free testosterone is converted to dihydrotestosterone and estrogen. Levels of dihydrotestosterone have been positively correlated with the frequency of orgasm in healthy men [3]. Hyposexuality in men without epilepsy is associated with a relatively broad range of reported hormone abnormalities, which appear to be related to the source of patient referrals (endocrinology, psychiatry, or urology clinics) and include low testosterone levels in 4 to 28% of patients and high PRL levels in 0 to 8% [4]. Establishing the relationship between altered sexuality and circulating hormone concentrations helps define the scope of the problem in patients with epilepsy. We can draw some conclusions about that relationship from studies of circulating hormone levels, the activity of the HPA, and sexual dysfunction.

3. Effects of epilepsy and its treatment on the HPA

The hypothalamus regulates release of end-organ hormones such as testosterone and estrogen by secreting GnRH, which regulates bursts of FSH and LH. These hormones then stimulate the ovaries or the Leydig cells of the testes to produce end-organ hormones such as estrogen and testosterone. Testosterone is converted into dihydrotestosterone and estrogen, which provide feedback regulation of the future production of GnRH. In addition, circulating levels of PRL are modified by the activities of the HPA.

A number of reports have highlighted the alterations in the HPA that are seen in patients with epilepsy (Table 1) [5–19,21]. Possibly the first articles to raise this issue were those of Herzog et al. [5]. This initial work described altered functioning of the HPA, as indicated by abnormal LH responses to infusion of GnRH, in 5 of 7 consecutive patients with temporal lobe epilepsy. One of the earliest articles chronicling the long-term effect of antiseizure therapy was that of Franceschi et al. in 1984 [6]. This study of 33 men and 29 women with epilepsy, who were all taking antiepileptic drugs (AEDs), and healthy volunteers showed that both basal and stimulated levels of PRL were increased in men with epilepsy. In women with epilepsy this effect was more variable and less marked. A key finding was that the changes were seen with all AEDs except valproic acid (VPA) and were more prominent with polytherapy. The changes did not appear to the investigators to be related to epilepsy itself.

Bonuccelli et al. [7] studied the effect of carbamazepine (CBZ) on PRL secretion in healthy volunteers and patients with epilepsy. These investigators did not document any CBZ-associated change in the normal circadian fluctuations of PRL secretion in healthy subjects or patients with epilepsy treated with CBZ, nor did they find any change in thyrotropin-releasing hormone (TRH)-stimulated PRL secretion.

Dana-Haeri et al. [8] evaluated pituitary responsiveness in 19 patients with epilepsy receiving long-term CBZ or phenytoin (PHT) therapy and 14 healthy control subjects. Baseline PRL levels were normal in the patients with epilepsy, and PRL levels 2 hours after stimulation with GnRH and TRH were slightly but significantly higher in women taking CBZ than in controls; no other changes were observed. Baseline LH levels were elevated in male patients with epilepsy, and the LH response to GnRH–TRH stimulation was exaggerated in all patients taking CBZ. The authors concluded that patients taking enzyme-inducing agents had an exaggerated LH response that might be related to a positive feedback mechanism.

Toone et al. [9] reported that LH, FSH, and PRL levels were elevated in 72 male patients with epilepsy who were receiving long-term AED therapy, and that the elevations were observed predominantly in patients taking enzyme-inducing agents. Rodin et al. [10] reported in 1984 that 33 male patients with epilepsy had significantly higher mean levels of FSH, LH, and PRL and nonsignificantly lower testosterone levels than 11 age-matched controls. These assessments were not followed up by a stimulation profile, but the authors identified clinical correlates of these hormone levels. Using the Bear–Fedio Personality Inventory, they showed that patients who reported depressed sexual arousal had significantly lower testosterone levels than those who did not. Elevated LH levels were correlated with an earlier onset of epilepsy. Increased PRL levels appeared to be associated with the use of CBZ. Elevated PRL levels also were associated with tonic–clonic seizures, but only in patients experiencing no other seizure type.

Another study looking at impairment of the HPA was that of Macphee et al. [11]. Circulating LH, FSH, and PRL levels were measured in 53 postpubertal male patients with epilepsy who were younger than 45 years and an age-matched control group of 14 untreated patients with epilepsy and 26 unmedicated healthy subjects. Basal LH levels were found to be elevated in the treated patients. In a subgroup of patients who underwent pituitary stimulation testing with GnRH and TRH, no differences were documented between patients with epilepsy, both treated and untreated,