

# Reproductive effects of valproate, carbamazepine, and oxcarbazepine in men with epilepsy

J. Rättyä, MD; J. Turkka, MD, PhD; A.J. Pakarinen, MD, PhD; M. Knip, MD, PhD; M.A. Kotila, MD, PhD; O. Lukkarinen, MD, PhD; V.V. Myllylä, MD, PhD; and J.I.T. Isojärvi, MD, PhD.

**Article abstract**—*Background:* Recent observations have indicated that reproductive endocrine disorders are common among women taking valproate (VPA) for epilepsy, but it is not known whether respective abnormalities develop in men taking VPA for epilepsy. Carbamazepine (CBZ) may induce endocrine disorders in men with epilepsy, but the endocrine effects of oxcarbazepine (OXC) are not known. *Methods:* Reproductive endocrine function was evaluated in 90 men taking VPA (n = 21), CBZ (n = 40), or OXC (n = 29) as monotherapy for epilepsy and in 25 healthy control men. *Results:* Twelve men (57%) taking VPA had increased serum androgen levels. The mean serum level of androstenedione was high in patients taking VPA. Serum levels of dehydroepiandrosterone sulfate were low, and serum concentrations of sex hormone-binding globulin (SHBG) were high in men taking CBZ. The endocrine effects of OXC seemed to be dose-dependent, because serum hormone levels were normal in patients with low OXC doses (<900 mg/day), but serum concentrations of testosterone, gonadotropins, and SHBG were high in patients with a daily OXC dose  $\geq$ 900 mg. *Conclusions:* VPA increases serum androgen concentrations in men with epilepsy. The endocrine effects of CBZ and OXC were different, because CBZ appears to decrease the bioactivity of androgens, whereas OXC does not.

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Reproductive endocrine disorders and sexual dysfunction have frequently been attributed to epilepsy itself, but antiepileptic drugs (AED) also have various effects on endocrine function.<sup>1–7</sup> Valproate (VPA) has been implicated to have only minor effects on the hormonal system in men with epilepsy.<sup>3,4</sup> However, there is growing evidence that VPA therapy induces endocrine disorders in women with epilepsy, which are characterized by hyperandrogenism and hyperinsulinemia that are related to obesity.<sup>5,6</sup>

Carbamazepine (CBZ) is one of the most widely used first-line AED. The use of CBZ is associated with a progressive increase in circulating levels of sex hormone-binding globulin (SHBG) and, consequently, in a decreased proportion of free, bioactive testosterone, which may result in sexual dysfunction in some men with epilepsy after long-term CBZ treatment.<sup>8</sup> CBZ-related endocrine changes have been attributed to the induction of the hepatic P450-enzyme system by the drug.<sup>9,10</sup>

Oxcarbazepine (OXC), a keto-derivative of CBZ, is a new AED that closely resembles CBZ in structure.<sup>11</sup> However, it has a different metabolic pathway in the liver; instead of by oxidation, it is mainly metabolized by reduction, and does not appear to induce the oxidative P450-enzyme system to the same extent as CBZ.<sup>12</sup> Previous studies have shown that the CBZ-induced changes in endocrine and met-

abolic function equilibrate after CBZ is replaced with OXC.<sup>13,14</sup> Thus, OXC has been suggested to be a safe AED with regard to endocrine and metabolic effects. However, there is evidence that OXC may also induce liver enzymes when prescribed at higher doses.<sup>15</sup> Endocrine effects of OXC have not been previously assessed in patients with epilepsy.

We sought to evaluate the reproductive endocrine effects of VPA, OXC, and CBZ in men with epilepsy. Special attention was paid to possible hyperandrogenism in men taking VPA for epilepsy and to the differences between endocrine changes related to CBZ and OXC treatment.

**Patients and methods.** The study was performed in the Outpatient Departments of Neurology, Oulu and Helsinki University Hospitals, Finland, with the approval of the local ethics committees, according to the principles of the Declaration of Helsinki.

*Subjects.* Patients considered for the study were men, aged 18 to 50 years, who were taking VPA, CBZ, or OXC for epilepsy in the Oulu University Hospital during the years 1995 to 1996 (n = 341). Patients with diseases other than epilepsy, patients who were taking regular medication in addition to AED, or receiving polytherapy for epilepsy were excluded. Furthermore, six consecutive men taking VPA for epilepsy were recruited for the study from the Outpatient Department of Neurology, Helsinki University Hospital over the first 6 months in 1998 due to the

From the Departments of Neurology (Drs. Rättyä, Turkka, Myllylä, and Isojärvi), Clinical Chemistry (Dr. Pakarinen), and Urology (Dr. Lukkarinen), University of Oulu; Medical School (Dr. Knip), University of Tampere; and Department of Neurology (Dr. Kotila), University of Helsinki, Finland.

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Address correspondence and reprint requests to Dr. Johanna Rättyä, Department of Neurology, University of Oulu, Finland, Kajaanintie 50, FIN-90220 Oulu; e-mail: johanna.rattya@oulu.fi

**Table 1** Clinical characteristics of study patients

AED	Patients, n	Age, y	Age at epilepsy diagnosis, y	Epilepsy type			Duration of current therapy, y	Drug dose, mg/d	Serum concentration of AED
				G	L	LG			
VPA	21	30.4 (20.0–48.0)	18 (3–34)	10	1	10	5.2 ± 3.0	1,219 ± 413	59.9 ± 21.2 mg/L
CBZ	40	34.5 (19.1–50.2)	18 (0.5–3.8)	4	3	33	8.8 ± 6.6	641 ± 183	6.5 ± 2.2 mg/L
OXC	29	30.0 (17.7–49.8)	18 (0–41)	8	3	18	2.4 ± 1.6	1,071 ± 439	11.4 ± 4.9 µg/L

Values are means (range or ± SD), except for type of seizure.

AED = antiepileptic drug; VPA = valproate; CBZ = carbamazepine; OXC = oxcarbazepine; G = generalized epilepsy; L = localization-related epilepsy without generalization; LG = localization-related epilepsy with generalized seizures.

limited number of VPA-treated patients available at the Oulu University Hospital. Eventually, 90 men agreed to participate in the study. Twenty-one of these patients were taking VPA, 40 were taking CBZ, and 29 were taking OXC as monotherapy. Informed consent was obtained from all patients. The clinical characteristics of the patients are given in table 1. Epilepsy type was classified according to the recommendations of the International League Against Epilepsy.<sup>16</sup> The classification was based on EEG findings and clinical features of seizures. The antiepileptic medication was prescribed according to generally recommended guidelines; CBZ or OXC were the drugs used particularly in partial seizures, whereas VPA was primarily used in primary generalized seizures.<sup>17</sup> The control group comprised 25 healthy men, who were recruited from the occupational health service of the Valtion Rautatiet railways. Their mean age was 35.9 (32.0 to 45.6) years.

**Methods.** All participants were clinically examined by one of the authors (J.I., J.R., J.T., or M.A.K.). The medical histories were obtained by interviewing patients and reviewing their hospital records. A structured interview regarding the sexual functions was carried out. A questionnaire regarding sexual functions included questions about the following: regular sexual relationship—1) yes, 2) no; infertility—1) yes, 2) no; changes in general interest toward sexuality during the last years—1) no change, 2) increased, 3) diminished; changes in libido during the last years—1) no change, 2) increased, 3) decreased; erectile dysfunction—1) yes, 2) no; frequency of erections—1) normal, 2) increased, 3) decreased; satisfaction with erection and orgasm—1) normal, 2) increased, 3) diminished. Sexual function was considered enhanced if the patient reported increased libido, potency, or satisfaction with erection and orgasm, and diminished if the patient reported no interest in sex or decreased libido, potency, or satisfaction with erection and orgasm. Otherwise, sexual function was considered normal.

Height was measured to the nearest 5.0 mm with a Harpenden wall-mounted stadiometer (Holtain Ltd., Crymth, Dyfed, UK), and weight was measured to the nearest 0.5 kg. Body mass index (BMI) was calculated (weight in kg/square of the height in m). Two blood samples were drawn (at 8.00 AM and at 8.30 AM) after an overnight fast for the analysis of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, androstenedione (ADION), dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS), estradiol (E<sub>2</sub>), SHBG, prolactin, and progesterone. Owing to pulsatile secretion of

gonadotropins, serum levels were analyzed from both blood samples, and the serum LH and FSH levels used in the results represent the mean value. Other hormones were analyzed from only the first sample. Plasma concentrations of insulin-like growth factor-I (IGF-I), and serum levels of insulin and IGF-binding proteins (BP) 1 (IGFBP-1) and 3 (IGFBP-3) were also measured in all participants.

**Assays.** Serum samples were frozen at -20 °C until analyzed. The concentrations of serum testosterone and E<sub>2</sub> were measured by a radioimmunoassay (RIA) kit obtained from Orion Diagnostica (Turku, Finland). Before the RIA, the serum samples were extracted with diethyl ether/ethyl acetate (9:1). Sensitivity of the testosterone assay was 0.07 ng/mL, the intra-assay coefficient of variation was 4.5%, and the interassay coefficient of variation was 6.4%. Values for the E<sub>2</sub> assay were 1.4 pg/mL (sensitivity), 4.5% (intra-assay coefficient), and 4.1% (interassay coefficient). The concentrations of free testosterone, DHEA, DHEAS, and ADION were assayed with RIA using kits from Diagnostic Products Co. (Los Angeles, CA). The serum samples were extracted with diethyl ether before the ADION assays and with dichloromethane before the DHEA assays. The sensitivity of the free testosterone assay was 0.15 ng/mL, the intra-assay variation was 3.8%, the interassay variation was 4.2%. Values were 0.04 ng/mL (sensitivity), 5.2% (intra-assay coefficient), and 5.6% (interassay coefficient) for the DHEA assay; 0.02 µg/mL (sensitivity), 4.5% (intra-assay coefficient), and 5.5% (interassay coefficient) for the DHEAS assay; and 0.02 ng/mL (sensitivity), 5.0% (intra-assay coefficient), and 8.6% (interassay coefficient) for the ADION assay. The concentrations of serum progesterone and prolactin were measured by the Chiron Diagnostics ACS:180 automated chemiluminescence system using the ACS:180 analyzer. Sensitivity of the progesterone assay was 0.16 ng/mL, the intra-assay variation was 4.6%, and the interassay variation was 7.5%. Values for the prolactin assay were 0.3 ng/mL (sensitivity), 2.1% (intra-assay coefficient), and 5.4% (interassay coefficient). Serum FSH, LH, and SHBG concentrations were measured by two-site fluoroimmunoassay methods with kits obtained from Wallac Ltd. (Turku, Finland). Sensitivity of the FSH assay was 0.03 mIU/mL, the intra-assay variation was 1.4%, and the interassay variation was 2.6%. Values for the LH assay were 0.03 mIU/mL (sensitivity), 2.3% (intra-assay coefficient), and 4.2% (interassay coefficient); and for the SHBG assay 0.07 µg/mL (sensitivity), 6.7% (intra-assay coefficient), and 8.0% (interassay coefficient). Serum insulin concentrations were measured by ELISA.<sup>18</sup> Sensitivity of the assay was 0.05 mU/L, intra-assay varia-

tion was less than 7.5%, and interassay was less than 9.3%. Plasma IGF-I levels were analyzed with a commercial RIA kit (Incstar, Stillwater, MN). The plasma samples were extracted with acid ethanol before the assay. Sensitivity of the assay was 7.6 ng/mL, with an intra-assay coefficient of variation of 5.1%, and an interassay coefficient of variation of less than 12%. Serum IGFBP-1 concentrations were measured with an enzymometric modification of an immunoradiometric method using a monoclonal antibody (MoAb 6035), with a sensitivity of 0.04 µg/L, an intra-assay variation of less than 4%, and an interassay variation of less than 10%. The total concentrations of free IGFBP-1 and IGFBP-1 bound to IGF-I were determined with this RIA. Serum IGFBP-3 concentrations were measured with a specific RIA kit (Diagnostic Systems Laboratories, Webster, TX). Sensitivity was 30 µg/L, the intra-assay variation was less than 5%, and the interassay variation was less than 9%.

Serum VPA and CBZ concentrations were assayed by a fluorescence polarization immunoassay system (AxSym analyzer, Abbott Diagnostic Division, Irving, TX). Sensitivity of the VPA assay was 0.58 mg/L, the intra-assay coefficient of variation was 1.8%, and the interassay coefficient of variation was 2.7%. Values for the CBZ assay were 0.2 mg/L (sensitivity), 1.2% (intra-assay coefficient), and 3.2% (interassay coefficient). Serum concentrations of monohydroxy-CBZ were determined by high-pressure liquid chromatography.<sup>19</sup> Sensitivity of the assay was 0.02 mg/L, and the intra-assay and interassay variations were below 5%.

The free androgen index (FAI) was calculated from the following formula: FAI = 100 × serum testosterone (nmol/L)/serum SHBG (nmol/L). Reference ranges of testosterone, ADION, DHEAS, and FAI were defined as the mean ± 2 SD in the control subjects (the effect of age was excluded by the analysis of covariance).

**Statistical analysis.** Because the mean age of the control subjects was higher than the age of the patients, the data were analyzed by analysis of covariance in order to exclude the effects of age on serum hormone levels. Differences in the frequency of sexual dysfunction or high serum androgen concentrations between various patient groups and control subjects were analyzed by the  $\chi^2$  test. The independent *t*-test was used for comparisons between patients taking VPA with high serum androgen concentrations and those with normal serum levels of androgens. It was also utilized for comparisons between CBZ- and OXC-treated patients with high or low daily drug doses.

**Results.** Results are presented in tables 2 through 4. Table 2 presents the prevalence of sexual dysfunction in patients and in control men. Four of five men taking OXC and the man taking VPA with decreased sexual function were previously taking CBZ, and according to the hospital records, sexual dysfunction had already developed during CBZ treatment in two of these patients. Low FAI values (<45) were reported in four men taking CBZ and three men taking OXC who reported decreased sexual functions. One man taking VPA, who reported increased sexual function, had high FAI value (110), but FAI values were normal in other patients with sexual dysfunction.

Elevated serum androgen levels (serum testosterone, ADION, or DHEAS concentration above the reference range) were observed in 12 (57%; *p* < 0.001) patients taking VPA, whereas only eight (20%; *p* = NS) of the CBZ-

treated men, seven (24%; *p* = NS) of the OXC-treated men, and two (8%) of the control subjects had high serum testosterone, ADION, or DHEAS levels.

The hormonal data are presented in tables 3 and 4. The data of DHEA, E<sub>2</sub>, prolactin, free testosterone, E<sub>2</sub>/T, and FAI are not shown when no differences between the patients and the control subjects were found. Patients taking VPA for epilepsy had higher mean serum ADION concentration and lower serum progesterone levels than the control subjects, but mean serum levels of other steroid hormones (testosterone, free testosterone, E<sub>2</sub>, DHEA, DHEAS), and mean serum prolactin, LH and SHBG levels, and FAI ratio were similar between men taking VPA and control men (see table 3). The E<sub>2</sub>/T ratio was higher (4.2 ± 1.3 versus 3.3 ± 1.5; *p* = 0.04) and the mean serum concentrations of FSH were lower for men taking VPA than for control men. Circulating insulin levels were higher in men taking VPA than in the controls, despite their comparable BMI (see table 4). There were no differences in circulating concentrations of IGF-I, IGFBP-1, or IGFBP-3 between men taking VPA and control subjects.

The VPA-treated patients with high serum androgen concentrations were more obese than patients taking VPA with normal serum androgen levels. Furthermore, serum E<sub>2</sub> and SHBG concentrations were higher in VPA-treated men with high serum androgen levels than in VPA-treated men with normal serum androgens (E<sub>2</sub>: 24.5 ± 7.3 versus 16.3 ± 6.7 pg/mL; SHBG: 3.8 ± 1.5 versus 2.3 ± 0.7 µg/mL; *p* = 0.01 for both). Serum IGFBP-1 levels also tended to be higher (*p* = 0.08) in VPA-treated men with high serum androgen levels than in the other men taking VPA, but their serum levels of gonadotropins as well as circulating concentrations of insulin, IGF-I, and IGFBP-3 were similar.

Patients taking CBZ for epilepsy had higher mean serum SHBG concentrations than control subjects. Serum levels of DHEAS were lower, FAI values tended to be lower (51 ± 17 versus 57 ± 14; *p* = 0.08), and circulating levels of insulin and IGF-I were higher in patients taking CBZ than in controls. However, the circulating concentrations of other hormones studied were not significantly different between patients taking CBZ and controls. The mean BMI was similar in men taking CBZ and in controls. Most of the endocrine effects of CBZ were not dose dependent, but serum prolactin levels were lower in CBZ-treated patients

**Table 2** Sexual function in men with epilepsy

Study group	Sexual function		
	Normal	Enhanced	Diminished
Valproate (n = 21)	16 (76)	4 (19)	1 (5)
Carbamazepine (n = 40)	30 (75)	3 (8)	7 (18)
Oxcarbamazepine (n = 29)	23 (80)	1 (3)	5 (17)
Control (n = 25)	22 (88)	1 (4)	2 (8)

Values are expressed as n (%).

Sexual function was considered enhanced if the patient reported increased libido, potency, or increased satisfaction with erection and orgasm, and diminished if the patient reported no interest in sex or decreased libido, potency, or decreased satisfaction with erection and orgasm. Otherwise, sexual function was considered normal.



**Table 3** Serum hormone concentrations in patients taking valproate (VPA), carbamazepine (CBZ), or oxcarbazepine (OXC) for epilepsy, and in control subjects

Medication group	n	T, ng/mL	DHEAS, $\mu$ g/mL	ADION, $\mu$ g/L	LH, U/L	FSH, U/L	PROG, ng/mL	SHBG, $\mu$ g/mL
VPA	21	5.6 $\pm$ 2.7	2.9 $\pm$ 1.6	3.7 $\pm$ 1.7*	3.4 $\pm$ 1.6	2.7 $\pm$ 1.0†	0.44 $\pm$ 0.31†	3.2 $\pm$ 1.4
CBZ	40	6.6 $\pm$ 3.0	1.6 $\pm$ 1.0*	2.3 $\pm$ 0.9	4.4 $\pm$ 1.8	5.5 $\pm$ 4.1	0.50 $\pm$ 0.35	4.2 $\pm$ 2.0†
OXC	29	7.0 $\pm$ 2.1	2.7 $\pm$ 0.8	2.6 $\pm$ 0.9	5.2 $\pm$ 3.9	6.5 $\pm$ 5.9	0.63 $\pm$ 0.22	3.9 $\pm$ 1.6
Control	25	5.7 $\pm$ 1.8	2.8 $\pm$ 1.0	2.2 $\pm$ 0.7	4.0 $\pm$ 1.3	4.4 $\pm$ 2.2	0.53 $\pm$ 0.28	3.2 $\pm$ 1.5

Values are mean  $\pm$  SD.

Patients were compared to control subjects by analysis of covariance.

\*  $p < 0.001$ ; †  $p < 0.05$ .

T = testosterone; DHEAS = dehydroepiandrosterone; ADION = androstendione; LH = luteinizing hormone; FSH = follicle-stimulating hormone; PROG = progesterone; SHBG = sex hormone-binding globulin.

with daily doses  $>600$  mg/day (7.0  $\pm$  2.6  $\mu$ g/L) than in patients with a daily dose of 600 mg or less (10.4  $\pm$  5.3  $\mu$ g/L;  $p = 0.01$ ).

Circulating levels of insulin and IGF-I were higher in men taking OXC for epilepsy than in the control men, but there were no significant differences in serum concentrations of other hormones studied between the patients taking OXC and control subjects. The serum concentrations of testosterone, LH, and SHBG tended to be higher in the OXC-treated men than in controls ( $p = 0.08$  [testosterone], 0.07 [LH], and 0.08 [SHBG]). Otherwise, patients with a daily OXC dose of less than 900 mg had similar serum hormone concentrations to those of control subjects, but their circulating levels of insulin and IGF-I were higher ( $p = 0.01$  for both). Patients with a high daily OXC dose ( $\geq 900$  mg/day) had increased levels of serum testosterone (7.5  $\pm$  2.1 ng/mL;  $p = 0.008$ ), free testosterone (78  $\pm$  11 pmol/L;  $p = 0.009$ ), LH (5.3  $\pm$  4.3 U/L;  $p = 0.003$ ), FSH (6.1  $\pm$  5.1 U/L;  $p = 0.02$ ), and SHBG (4.2  $\pm$  1.6  $\mu$ g/mL;  $p = 0.005$ ) when compared with control subjects (hormone values of control subjects are presented in table 3, except free testosterone [66  $\pm$  11 pmol/L]). The mean daily OXC dose was 1,286 ( $\pm 449$ ) mg in the men with high serum androgen levels, and not one of these patients had an OXC dose of less than 900 mg/day. Men with normal serum androgen levels re-

ceived a mean daily OXC dose of 1,002 ( $\pm 422$ ) mg. However, the difference in daily OXC dose between patients with high and normal androgen levels was not significant (see tables 3 and 4).

**Discussion.** All AED studied were associated with noticeable changes in the reproductive endocrine function in men with epilepsy. Increased serum androgen levels were found in close to 60% of the men taking VPA. CBZ had an opposite effect on the androgen balance in men with epilepsy; serum levels of DHEAS were low, and SHBG concentrations were high in men taking CBZ. Moreover, 18% of men taking CBZ for epilepsy reported decreased libido, impaired potency, or both. Low daily OXC doses did not have any effects on serum concentrations of reproductive hormones, but men taking high doses of OXC had increased serum testosterone, gonadotropin, and SHBG levels. Serum insulin levels were high in all patient groups.

In previous studies, VPA was considered a safe AED from an endocrine point of view in men with epilepsy, but the number of VPA-treated patients in these surveys has been limited.<sup>3,4</sup> In the current

**Table 4** Body mass index (BMI), serum levels of insulin, insulin-like growth factor binding proteins 1 and 3 (IGFBP-1 and -3), and plasma levels of insulin-like growth factor I (IGF-I) in men taking valproate (VPA), carbamazepine (CBZ), or oxcarbazepine (OXC) for epilepsy, and in control subjects

Group	n	BMI, kg/m <sup>2</sup>	Insulin, mU/L	IGFBP-1, $\mu$ g/L	IGF-I, ng/mL	IGFBP-3, mg/L
VPA	21	25.1 $\pm$ 2.9	10.9 $\pm$ 11.7*	2.4 $\pm$ 2.1	156 $\pm$ 30	3.1 $\pm$ 0.5
With high serum androgen levels	12	26.2 $\pm$ 3.2†	8.4 $\pm$ 4.9	3.0 $\pm$ 2.6	153 $\pm$ 30	3.0 $\pm$ 0.6
With normal serum androgen levels	9	23.7 $\pm$ 1.9	9.5 $\pm$ 9.9	1.5 $\pm$ 0.9	157 $\pm$ 32	3.3 $\pm$ 0.8
CBZ	40	25.3 $\pm$ 3.6	6.8 $\pm$ 4.2‡	3.5 $\pm$ 2.9	156 $\pm$ 37*	3.0 $\pm$ 0.6
OXC	29	24.4 $\pm$ 3.2	5.5 $\pm$ 2.6*	2.8 $\pm$ 2.1	163 $\pm$ 43†	3.2 $\pm$ 0.7
Control	25	24.1 $\pm$ 1.9	3.2 $\pm$ 2.0	3.0 $\pm$ 2.2	131 $\pm$ 34	3.0 $\pm$ 0.5

Values are mean  $\pm$  SD.

Data are also compared between men with high serum androgen levels taking VPA and those with normal serum androgen levels. Patients with epilepsy are compared to control subjects by analysis of covariance, except that patients with high serum androgen levels taking VPA are compared to those with normal serum androgens by independent *t*-test.

\*  $p < 0.01$ ; †  $p < 0.05$ ; ‡  $p < 0.001$ .

study, VPA treatment clearly affected the reproductive hormone balance in men. The mean serum level of ADION was high in VPA-treated men, and furthermore, more than half of the patients taking VPA had serum levels of testosterone, ADION, or DHEAS above the reference range, which is comparable with the prevalence of hyperandrogenism reported in adult women and young girls taking VPA for epilepsy.<sup>5,6,20</sup> The serum concentration of ADION tended also to be high in a previous study in men taking VPA.<sup>3</sup> In the current study, serum levels of FSH were low in VPA-treated men, which is consistent with a previous observation.<sup>4</sup> Furthermore, the mean serum concentration of LH tended to be low in VPA-treated men in this study. In previous studies, serum LH levels has reported to be low<sup>4</sup> or unchanged<sup>3</sup> in men taking VPA. As is well established, pituitary gonadotropin secretion is controlled by a negative feedback system (i.e., increased levels of testosterone inhibit the release of gonadotropins).<sup>21</sup> Theoretically, the decreased serum levels of LH in VPA-treated men could be related to the activation of this negative feedback mechanism as a consequence of excess testosterone production stimulated by VPA. However, in this study there were no differences in serum gonadotropin concentrations between VPA-treated patients with normal serum androgen levels and those with high serum androgen levels. It is possible that the effects of VPA on androgen production in men may be modified by an inhibitory feedback regulation of androgen biosynthesis.

Obesity and hyperandrogenism appear to be associated with hyperinsulinemia and altered circulating levels of IGF-I, IGFBP-1, and IGFBP-3 in women taking VPA for epilepsy.<sup>5,6</sup> In the current study, men taking VPA with high serum androgen concentrations were also more obese than those with normal serum androgen levels, although obese men in general have lower serum androgen concentrations than men of normal weight.<sup>22</sup> We could not demonstrate any differences in circulating levels of insulin, IGF-I, and IGFBP-3 between VPA-treated men with normal serum androgen levels and those with high serum androgen levels. In our previous study, hyperandrogenemia was common among young girls (aged 8 to 18 years) taking VPA for epilepsy, but the girls with hyperandrogenemia were not hyperinsulinemic, though their BMI tended to be higher than that of the control girls.<sup>20,23</sup> Therefore, in men and young girls, VPA-related hyperandrogenism is not associated with hyperinsulinemia, nor is it induced by increased LH stimulation. Accordingly, VPA-related hyperandrogenism does not seem to be mediated through changes in the serum concentrations of other hormones. This implies that hyperandrogenism may be the primary VPA-related endocrine abnormality, and that other hormonal and metabolic changes as well as weight gain could be either secondary consequences of hyperandrogenism or unrelated phenomena. One potential explanation for VPA-related hyperandrogenism is a peripheral effect

of VPA on androgen synthesis or metabolism. Actually, VPA is a well-known enzyme inhibitor.<sup>9</sup>

The current results confirm the findings of previous studies on the endocrine effects of CBZ; serum concentrations of DHEAS were low, FAI values tended to be low, and serum levels of SHBG were high during CBZ treatment.<sup>1,8</sup> Serum levels of DHEA—as well as of other hormones analyzed—were normal in CBZ-treated patients. The endocrine effects of CBZ have been suggested to be due to an accelerated metabolism of hormones or stimulated production of binding proteins (e.g., SHBG) in the liver as a consequence of hepatic enzyme induction during CBZ treatment. Serum concentrations of free, bioactive testosterone decrease in patients taking CBZ due to increased serum SHBG levels, and the biologic function of testosterone may diminish. CBZ induces these hormonal disorders even at low daily doses ( $\leq 600$  mg/day).

The endocrine effects of OXC have previously been studied only in men with epilepsy switching their medication from CBZ to OXC. Replacement of CBZ by OXC resulted in a restoration of normal circulating levels of SHBG and DHEAS contemporaneously with a decrease in the induction of the hepatic P450 enzyme system.<sup>13</sup> However, in the previous study, mean daily OXC doses were lower than in our current survey ( $913 \pm 251$  versus  $1070 \pm 440$  mg/day).<sup>13</sup> Observations in the current study suggest that reproductive endocrine changes are seen in men taking high daily doses of OXC. Mean serum levels of testosterone and SHBG were high in patients taking high daily OXC doses. However, their FAI ratios were normal, suggesting normal bioactivity of testosterone. Conversely, the serum concentrations of reproductive hormones in patients with an OXC dose lower than 900 mg/day were similar to those of the control subjects. Therefore, CBZ and OXC medications seem to have different effects on endocrine function, because CBZ diminishes the bioactivity of androgens.

Although OXC is not as potent an inducer of liver enzymes as CBZ, there is evidence that OXC may still function as an enzyme inductor with a sufficient dosage.<sup>15</sup> Moreover, it is possible that OXC may induce different isoenzymes of the hepatic microsomal cytochrome P450 enzyme system than CBZ, which may explain the differences in endocrine effects between these two drugs.

Circulating insulin and IGF-I concentrations were higher in patients treated with CBZ or OXC than in control men, which has not been reported before in men with epilepsy. These findings were not dose dependent. In our previous study, serum insulin and plasma IGF-I levels were high in young girls taking CBZ or OXC for epilepsy.<sup>23</sup> However, the pathomechanism and clinical significance of high circulating concentrations of these hormones are unclear.

Seven patients taking CBZ, five taking OXC, one taking VPA, and two control men reported impaired sexual function. In addition, four patients taking

VPA, four taking CBZ, and one taking OXC reported hypersexuality. Sexual dysfunction is a complicated disorder, which may be affected by, for example, psychological factors, life circumstances, epilepsy itself, and also hormonal factors. All except one of these patients had partial secondary generalized epilepsy, and sexual dysfunction and reproductive endocrine disorders has been reported to be common especially in men with partial epilepsy of temporal lobe origin.<sup>2</sup> Five of seven men taking CBZ reporting impaired sexual function had high serum SHBG concentration or low FAI ratio. This reflects reduced bioactivity of testosterone, which in general may be associated with decreased sexual function.<sup>8</sup> However, the serum androgen profiles were normal in the other patients with enhanced or diminished sexual function. Of the patients with sexual dysfunction, the patient taking VPA and four of five men taking OXC had previously taken CBZ for epilepsy. It is possible that sexual dysfunction in these men may be related to their previous CBZ treatment.

Each of the AED studied affected serum concentrations of reproductive endocrine hormones in men with epilepsy. Increased serum androgen levels were common in men taking VPA for epilepsy, but they were not associated with elevations in circulating LH or insulin concentrations. These results suggest that VPA may directly affect steroid synthesis or metabolism. OXC and CBZ seem to have different reproductive endocrine effects in men with epilepsy, despite their close structural homology. OXC does not appear to decrease the bioactivity of androgens, whereas CBZ does.

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J. Rättyä, J. Turkka, A. J. Pakarinen, et al.

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