Effects of some antiepileptic drugs on reproductive system

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ABSTRACT

Epilepsy is associated with reproductive disorders and decreased fertility. Some studies were evaluated on reproductive system, the effects of antiepileptic drug on women and on male fertility. Reproductive disorders were more common in women with idiopathic generalized epilepsy and in women taking valproate also in young age increased the risk of these disorders. Oxcarbazepine was associated with reproductive disorders in women with epilepsy. In men all antiepileptic drugs were associated with sperm abnormalities, and sperm abnormalities in men taking valproate were associated with decreased testicular volume. The epilepsy and antiepileptic drugs during adulthood decreased fertility. The reproductive endocrine effects of AEDs should be taken into consideration when prescribed to fertile aged men and women, especially, if the duration of treatment is long.

INTRODUCTION

Epilepsy affects about 20-40 million people worldwide. It is more common in children than adults, with an incidence of about eight per 1000 children under the age of seven years. Epilepsy is the second most common neurological disorder, after stroke. Epilepsy is a common neurological disorder that consists of a wide variety of symptoms arising from abnormal, excessive or synchronous neuronal activity in the brain (Engel and Pedley 1997). In most cases, it begins before adulthood or after 50 years of age (Hauser 1997). The classification of epilepsy is based on the etiology and the type of seizures. As a chronic disease, epilepsy can continue for years or even a lifetime so long-term medication is needed. Surgical treatment has become a treatment option and the spectrum of antiepileptic drugs (AEDs) which allows the selection of an optimal AED for a specific epilepsy syndrome. A typical seizure may include brief and periodic episodes of change in the normal state of consciousness, loss of muscle tone, sensory and behavioral alterations. Seizures are caused by “occasional, sudden, excessive, rapid, and local discharge of gray matter” and a generalized convulsion resulted when normal brain tissue is invaded by the seizure activity initiated in the abnormal focus. Seizure may be associated with presence of an infection, tumor, stroke, or birth injury. However, in other cases, it may be associated with a biochemical and/or physiological defect in the brain presumably due to an imbalance of excitatory and inhibitory neurotransmitters. This imbalance of neurotransmitters may be a result of structural pathology or genetic factors or stress (Wagh et al., 2011; Porter and Meldrum, 2001; Gerlach and Krajewski, 2010). The various side-effects of AEDs has increased which makes it possible to adapt the medication to

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the needs of individual patients and thus improve compliance (Shorvon, 2004). The roles of epilepsy and AEDs in contributing to reproductive endocrine disorders in people with epilepsy are still widely debated. Epilepsy itself may disturb the regulation of secretion of reproductive hormones. The AEDs are to induce reproductive endocrine disorders. It is known that valproate (VPA) is associated with reproductive disorders and obesity in women with epilepsy (Isojärvi et al., 2001, Betts et al., 2003). Active epilepsy during fertile age may predispose to reproductive dysfunction and possible infertility (Mikkonen et al., 2004b) and may decreased fertility in epileptic patients (Wallace et al., 1998, Artama et al., 2004). The role of epilepsy and AEDs in the development of reproductive disorders in epileptic patients.

A typical therapeutic strategy is to optimize the use of a single antiepileptic drug (AED), given that ~60% of patients have become seizure free using this approach. Unfortunately, only 5% of patients who fail to respond adequately to monotherapy experience long term freedom from seizures using polytherapy. The remaining patients are treatment-resistant in that seizures are not adequately controlled. The aim of AEDs therapy is to allow patients to maintain a normal lifestyle by control of seizures with lesser side effects. Phenobarbital (PBT), the first widely used AED, subsequent surge in AEDs such as PZPs, valproic acid and PHT was a direct consequence of the developments. However, many AEDs discovered and are associated with dose limiting side effects, adverse reactions and toxicity through drug-drug interactions. The realization that these early compounds could be further optimized for tolerability and properties has rational drug design efforts for development of subsequent AEDs. Generally AEDs modulate voltage-gated ion channels, facilitate inhibitory neurotransmission, attenuate excitatory neurotransmission and/or modulate synaptic release. The genetic associations with epilepsy, has facilitated a more recent target-based approach to novel AEDs (French et al., 2004a; French et al., 2004b; French et al., 2004c; Fisher et al., 2005; Birbeck et al., 2007).

ANTIEPILEPTIC DRUGS

Various AEDs (Dwivedi, 2001; Chisholm, 2005), some drugs were used in earliest time and some drugs are currently used. Available AEDs control seizures in about two thirds of the patients. In 1857, potassium bromide (KBr) was used for the treatment of epilepsy. PBT was introduced in 1912, and later, in 1938, PHT was used as AED. Drugs used in the treatment of two major seizure types, partial and generalized, are quite distinct in their clinical profiles. PBT was recognized as AED. Its usefulness was limited to generalized tonic clonic seizures, and to a lesser degree, simple and complex partial seizures and had no effect on absence seizures. PHT suppressed seizures in the absence of sedative effects. The electroshock seizure test is extremely valuable, because drugs that are effective against partial and tonic-clonic seizures in humans. Seizures induced by the chemo convulsant scPTZ, is most useful in identifying drugs that are effective against myoclonic (absence) seizures in humans. The chemical structures of most of the drugs introduced before 1965 were closely related to PBT included hydantoins and succinimides. Between 1965 and 1990, chemically distinct structures of PZPs, iminostilbene (CBZ), and branched-chain carboxylic acid (valproic acid) were introduced, followed in the 1990s by a phenyltriazine (LTG), cyclic analog of GABA (gabapentin), sulfamate-substituted monosaccharide (topiramate), nipeptic acid derivative (tiagabine), and pyrrolidine derivative (levetiracetam) (Mohanraj, and Brodie, 2003; French et al., 2004; Mohanraj and Brodie, 2003; Kwan and Sander, 2004; Lusczkzi, 2009; Najafi et al., 2011; Gerlach and Krajewski, 2010).

THERAPEUTIC ASPECTS

The ideal AEDs would suppress all seizures without causing any unwanted effects. Unfortunately, the drugs used currently not only fail to control seizure activity in some patients, but frequently cause unwanted effects that range in severity from minimal impairment of the CNS to death from aplastic anemia or hepatic failure. So the task for selecting the appropriate drug or combination of drugs that best controls seizures in an individual patient at an acceptable level of untoward effects (Asif, 2015a; Asif, 2015b). The degree of success varies as a function of seizure type, cause, and other factors. To minimize toxicity, treatment with a single drug is preferred. If seizures are not controlled with the initial agent at adequate plasma concentrations, substitution of a second drug is preferred to the concurrent administration of another agent. However, multiple-drug therapy may be required, especially when two or more types of seizure occur in the same patient. The ultimate therapeutic regimen must be determined by clinical assessment of effect and toxicity (Privitera et al., 2003). The major drugs for partial and generalized tonic-clonic seizures are PHT (or congeners), CBZ, VPA, and barbiturates. However, availability of newer drugs- LTG, gabapentin, oxcarbazepine, topiramate, vigabatrin, and levetiracetam is altering clinical practice (Porter, and Meldrum, 2001; Privitera et al., 2003; Rogawski and Loscher, 2004). For most AEDs, relationships between blood levels and therapeutic effects have been characterized to a high degree. The same is true for the pharmacokinetics of these drugs. These relationships provide significant advantages in the development of therapeutic strategies for the treatment of epilepsy. The therapeutic index for most AEDs is low, and toxicity is not uncommon. Thus, effective treatment of seizures requires an awareness of the therapeutic levels and pharmacokinetic properties as well as the characteristic toxicities of each agent. Measurements of AED plasma levels are extremely useful when combined with clinical observations (Chisholm, 2005; Bialer 2006; Birbeck et al., 2007).

DRUGS USED IN INFANTILE SPASMS

The treatment of infantile spasms is unfortunately limited to improvement of control of the seizures rather than other features of the disorder, such as retardation. Most patients receive intramuscular corticotropin, although some clinicians
note that orally prednisone may be equally effective. In either case, therapy must often be discontinued because of adverse effects. If seizures recur, repeat courses of corticotropin or corticosteroids can be given, or other drugs may be tried. Other drugs widely used are the PZPs such as CZP or nitrazepam, their efficacy in this heterogeneous syndrome may be nearly as good as that of corticosteroids. Vigabatrin may also be effective. The mechanism of action of corticosteroids or corticotropin in the treatment of infantile spasms is unknown.

GENERAL SIDE EFFECTS

Diarrhea, vomiting, upper respiratory tract infection, constipation, dyspepsia, ataxia, nervousness, allergic skin reaction, nausea, headache, dizziness, aplastic anemia, hepatic failure. The cognitive side effects of CBZ, PHT and VPA sodium are comparable and associated with modest psychomotor slowing accompanied by decreased attention and memory (Scheffer, and Berkovic. 2003; Wagh, et al., 2011; Asif M. 2016). Neuropsychological side effects generally emerge according to a dose dependent relationship; however, both quality of life and memory may be affected, even when serum blood concentrations are within standard therapeutic ranges. In children, drug effects are seen in decreased performance or memory. Some children are at heightened risk for developing disproportionate cognitive side effects with CBZ (Lynch et al., 2004; Bialer et al., 2004; Dwivedi, 2001; Edith et al., 2002; Fisher et al., 2005).

GENERAL ASPECTS OF EPILEPSY

Epilepsy is a common neurological disorder resulting from abnormal and excessive discharges of electrical activity of cerebral neurons. Epileptic seizures can evident as such symptoms as altered consciousness, involuntary movements, abnormal sensory phenomena, increased autonomic activity or transient disturbances of behavior depending on the localization of the epileptic disorder. Although epileptic seizures can be symptoms of a causative brain disease, in majority of cases of epilepsy cause is unknown (Engel & Pedley 1997). The prevalence of epilepsy is higher in the developing countries (Forsgren, 2004). The risk for epilepsy is highest during the first year of life and it decreases during childhood and adolescence, but in the age range of 50-60 years the risk for epilepsy starts to increase again. Approximately 50% of cases of epilepsy begin in childhood or adolescence (Hauser et al., 1997), but in other epidemiological studies 75-90% of cases of epilepsy have started before adulthood and is more often found in men (Hauser, 1997). All factors that cause pathological or functional changes in the brain may predispose to epilepsy. In adults trauma, brain tumors and vascular diseases of the brain are the most common causes of epilepsy, while in children metabolic defects, congenital malformations, infections, genetic diseases and perinatal injuries are among the common etiologies. However, the etiology of epilepsy remains unresolved in a large number of patients (Beghi 2004). Genetic factors can also predispose to epilepsy. In a majority of the cases epilepsy is caused by interactions of many genes and environment, and in a minority of cases of epilepsy can be recognized to a single gene disorder (Gutierrez-Delicado and Serratosa, 2004). Epileptic seizures can manifest under stressful conditions (sleep deprivation, alcohol or drug abuse, infections, hypoglycemia and metabolic changes) even in persons without epilepsy. Diagnosis of epilepsy is usually made after two or more unprovoked seizures (Moshe and Pedley, 1997).

TREATMENT

The aim in the treatment of epilepsy is to achieve complete seizure control. Even though AED treatment has improved remarkably in terms of efficacy and tolerability during the last decades, still 20-30% of epileptic patients suffer from drug resistant epilepsy (Hauser and Hesdorffer 2001). Surgical treatment should be considered in patients treated with appropriate AEDs for 2-3 years without sufficient response (Kalviainen and Keranen, 2006). Vagal nerve stimulator is a treatment option for drug refractory epilepsy patients who are not suitable candidates for respective epilepsy surgery (Schachter, 2004). If a specific affecting factor for seizures has been identified, the patients are recommended to avoid factors with tendency to trigger seizures (Perucca, 1996). In children febrile seizures are not usually considered an indication for antiepileptic treatment (Hirtz et al., 2003). Epileptic syndrome and seizure type should be identified before initiation of rational AED treatment in order to obtain the best possible efficacy and also to improve the prognosis. Some AEDs are efficacious in a certain condition, while some other AEDs may worsen the same condition (Genton et al., 2000). Usually, drug treatment for epilepsy is started after two unprovoked seizures. However in cases of abnormal interictal epileptic form electroencephalography (EEG) or of persisting predisposing cause for seizures or even when avoiding the unwanted physical or psychosocial consequences for seizures is especially important, medication can be initiated after one seizure (Hirtz et al., 2003). The early intervention may prevent the epileptic process from becoming chronic. Most epileptic patients achieve seizure freedom with monotherapy, in the majority of cases with the first or second appropriate AED that is tried. Fewer interactions and better compliance are some of the advantages of monotherapy. However, about one-third of patients suffers from more severe epilepsy and may need polytherapy (Kwan & Brodie, 2001). Polytherapy may give better seizure control, but it also increases the risk for interactions and side effects. About 25% of all patients do not respond to drug therapy. Drug refractoriness may be caused by false diagnosis or continuous or intermittent predisposal to factors that provoke seizures, such as sleep deprivation or alcohol abuse. (Keränen & Kälviäinen, 1997) After five years of adequate AED treatment about 70% of patients achieve reduction (Cockerell et al., 1997). Discontinuation of medication should be considered after 3-5 years of seizure freedom and if considered appropriate should be done slowly in order to
minimize the risk of relapse (Keränen et al., 1997). Some epileptic syndromes such as juvenile myoclonic epilepsy may need lifelong medication and the risk for relapse may also be high after discontinuation of medication in localization related epilepsy (LREs). Furthermore, drug discontinuation after seizure freedom resulted in relapse in one third of patients (Sillanpaa & Schmidt, 2006). A typical therapeutic strategy is to optimize the use of a single antiepileptic drug (AED), given that ~60% of patients have become seizure free using this approach. Unfortunately, only 5% of patients who fail to respond adequately to monotherapy experience long-term freedom from seizures using polytherapy. The remaining patients are treatment-resistant in that seizures are not adequately controlled. The AEDs therapy is to allow patients to maintain a normal lifestyle by control of seizures with lesser side effects. Phenobarbital (PBT), the first widely used AED, subsequent surge in AEDs such as PZPs, valproic acid and PHT was a direct consequence of the developments. However, many AEDs discovered and are associated with dose limiting side effects, adverse reactions and toxicity through drug-drug interactions. The realization that these early compounds could be further optimized for tolerability and properties has rational drug design efforts for development of subsequent AEDs. Generally AEDs modulate voltage-gated ion channels, facilitate inhibitory neurotransmission, attenuate excitatory neurotransmission and/or modulate synaptic release. The genetic associations with epilepsy, has facilitated a more recent target based approach to novel AEDs (French et al., 2005; Birbeck et al., 1997). Some studies that have compared the efficacy of novel AEDs (Wong et al., 1999, McDonald et al., 2005).

**BASIC PHARMACOLOGY OF AEDS**

AEDs can be classified into five very similar chemical groups: barbiturates, hydantoins, oxazolidinediones, succinimides, and acetylureas. These groups have in common a similar heterocyclic ring structure with a variety of substituents. For drugs with this basic structure, the substituents on the heterocyclic ring determine the pharmacologic class, either anti-MES or anti-PTZ. Very small changes in structure can dramatically alter the mechanism of action and biological properties of the compound. The remaining drugs-CBZ, valproic acid, and the PZPs are structurally dissimilar, as are the newer compounds marketed since 1990, ie, felbamate, gabapentin, LTG, oxcarbazepine, tiagabine, topiramate, vigabatrin, and levetiracetam. Existing AEDs provide adequate seizure control in about two thirds of patients. A fraction of the epileptic population is resistant to all available drugs. New AEDs are being sought not only by the screening tests noted above but also by more rational approaches. Compounds are sought that act by one of three mechanisms: (1) enhancement of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamatergic) transmission, or (3) modification of ionic conductances (He et al., 2004; Wagh et al., 2011; Porter and Meldrum, 2001; Gerlach and Krajewski, 2010).

**DRUGS USED IN PARTIAL & GENERALIZED TONIC-CLONIC SEIZURES**

The major drugs for partial and generalized tonic-clonic seizures are PHT (or congeners), CBZ, VPA, and barbiturates. However, availability of newer drugs- LTG, gabapentin, oxcarbazepine, topiramate, vigabatrin, and levetiracetam is altering clinical practice.

**Antiepileptic medication:** The efficacy of standard AEDs is well established and some differences in efficacy between VPA, phenytoin (PHT), carbamazepine (CBZ) (de Silva et al., 1996) and novel AEDs have been observed when these AEDs have been used for appropriate seizure types (Marson et al., 2007a, 2007b). However, there are only a few head-to-head studies that have compared the efficacy of novel AEDs (Wong et al., 1999, McDonald et al., 2005).

**Carbamazepine:** CBZ is the most commonly prescribed drug for epilepsy in Europe. It is the drug of choice in partial epilepsies with or without secondary generalization (Shorvon, 2000). It is chemically related to tricyclic antidepressants and blocks the sodium channels in neural membranes. CBZ has limited water solubility, and 75% of CBZ is bound to plasma proteins (Shorvon, 2000). CBZ is an inducer of the hepatic P450 enzyme system (Perucca et al., 2004), and it also induces its own metabolism. Therefore, higher doses are needed to maintain the plasma concentration in long-term therapy. Due to the hepatic induction, CBZ also has effects on the metabolism of endogenous and exogenous hormones. CBZ has pharmacokinetic interactions with other drugs. It increases the metabolism of ESM, VPA, LTG and BZP which results in accelerated elimination of these drugs. CBZ has also been reported to decrease the bioavailability of ethinyloestradiol and levonorgestrel used in contraceptive treatment. On the other hand, erythromycin inhibits the metabolism of CBZ and may increase the levels of CBZ to toxic levels (Dam & Christiansen, 1977). Neurological adverse effects are fairly often associated with the use of CBZ. Nystagmus, drowsiness, headache and ataxia are often seen. Nausea and rash are also common side effects of CBZ. More severe adverse effects of CBZ include effects on cardiac function, e.g. atrioventricular conduction delay and bradycardias and aplastic anemia, toxic hepatitis and Stevens-Johnson syndrome (Brodie & Dichter, 1996).

**Oxcarbazepine:** Oxcarbazepine (OXC) is a keto-analogue of CBZ, and its anticonvulsant efficacy is comparable to that of CBZ in partial seizures with or without secondary generalization. However, OXC has a different metabolic pathway and pharmacokinetic profile from those of CBZ. It is metabolized mainly by reduction to its active metabolite, 10,11-dihydro-10hydroxy-carbamazepine, which is responsible for its antiepileptic efficacy (Bang & Goa, 2003). The binding to plasma proteins is about 67% for OXC and 38% for 10,11-dihydro-10hydroxy-carbamazepine (Shorvon, 2000). The anticonvulsant action of OXC is mediated by...
blockage of sodium channels. OXC is considered to be better tolerated than CBZ due to its better pharmacokinetic profile and less potential to induce the liver P450 enzyme system. Elimination of OXC is increased by drugs that induce hepatic enzymes, e.g. CBZ, PHT and PB. In women OXC has been shown to reduce the efficacy of oral contraceptives by decreasing the serum concentrations of ethinylestradiol and levonorgestrel (Fattore et al., 1999). Adverse effects of OXC are usually mild e.g. dizziness, ataxia, headache, diarrhea, nausea and vomiting. Low serum sodium levels and hyponatremia may be associated with OXC treatment, they are reported to be more common in female patients and in elderly subjects.

**Valproate:** VPA was first used as a solvent for decades until its potential as an AED was discovered in 1963. VPA has a wide spectrum of antiepileptic efficacy and it is used in both LRE and IGE and also in childhood epilepsies. It is the drug of choice for generalized myoclonic epilepsy and absence seizures (Shorvon, 2000). VPA is also used in the treatment of bipolar mood disorder. Its exact antiepileptic mode of action is not known. However, it is assumed that it has multiple mechanisms of action to prevent seizures. VPA is known to affect the voltage-dependent sodium channels and neurotransmitters such as gamma-aminobutyric acid (GABA), and it may also have effect on glutamate transporters (Hassel et al., 2001). The protein binding of VPA is 90% in plasma and due to concentration dependent binding there is a curvilinear relationship between dose and plasma concentration. VPA does not induce the hepatic P450 enzyme system, but it is an enzyme inhibitor and inhibits the oxidative metabolism of PHT and ESM (Perucca et al., 2004). It is also known that CBZ and other AEDs with liver enzyme inducing properties can decrease serum VPA levels, while salicylates increase VPA blood levels. The adverse effects of VPA are well established. Gastro-intestinal effects such as nausea or diarrhea are common; also weight gain and neurological adverse effects such as tremor, fatigue and dizziness are often reported. These side effects appear early in the therapy and do not necessarily require dosage adjustments. Hepatotoxicity and hematologic changes, such as thrombocytopenia are more severe adverse effects of VPA Exposure to VPA during pregnancy predisposes to congenital malformations, and the risk is higher in women on polytherapy (Holmes et al., 2001, Wyszynski et al., 2005, Artama et al., 2005, Morrow et al., 2006). Maternal VPA therapy is also associated with impaired cognitive development and reduced verbal intelligence of the children exposed to VPA in utero (Barrett & Richens, 2003; Gaily et al., 2004).

**Other antiepileptic drugs:** PHT is one of the most frequently used AEDs in the world. It is considered effective, but it is currently a less frequently used AED because of its interaction potential and long-term side effects. It is an inducer of the hepatic P450 enzyme system. PHT is effective in the treatment of focal seizures with or without secondary generalization, and its anticonvulsant efficacy is based on blockage of the voltage dependent sodium channels. PHT has saturable kinetics which may lead to an unexpected increase in serum PHT concentration and related central nervous system side effects. Neurological side effects, gingival hypertrophy, nasea, depression, rash, blood dyscrasias and hepatotoxic effects are some of the side effects of PHT (Eadie, 2004). PHT may reduce the amount of bioactive sex steroids by inducing the synthesis of sex hormone binding globulin (SHBG) (Perucca et al., 2004). Lamotrigine (LTG) is a novel AED and is indicated for the treatment of partial and generalized epilepsies as adjunctive therapy or monotherapy, and also as adjunctive treatment in Lennox-Gastaut syndrome. It is a triazine compound which affects the sodium channels in addition to calcium channel blockage. 55% of LTG is bound to plasma proteins and it is metabolized in the liver and eliminated renally as a glucuronide. Liver enzyme inducing AEDs increase the metabolism of LTG and reduce its serum concentrations, whereas VPA inhibits the metabolism of LTG and increases its serum concentrations. Rash, nausea and dizziness are some of the most common side effects of LTG (Matsuo 2004). Stevens-Johnson syndrome and toxic epidermal necrolysis are rare but serious side effects of LTG (Schlienger et al., 1998). The prevalence of reproductive disorders have been decreased in epileptic patients using LTG when compared to epilepsy patients using liver enzyme-inducing antiepileptic drugs or VPA (Morrell et al., 2003, Herzog et al, 2004).

**Reproductive endocrine system**

**Hypothalamic-pituitary unit:** The pulsatile secretion of hypothalamic hormones is controlled by neurotransmitters and by concentrations of hormones which are secreted in peripheral glands by feedback mechanism. The hypothalamus secretes regulatory hormones into portal vessels, where they are transported to the pituitary. The secretion of each pituitary hormone is regulated by at least one of the hypothalamic hormones, and the hormones from peripheral endocrine glands also control the secretion of pituitary hormones by the feedback mechanism. Anterior pituitary secretes luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropin (ACTH), thyrotropin, growth hormone (GH) and prolactin, and posterior pituitary releases antiuretic hormone and oxytocin, which are secreted in the supraoptic and paraventricular nuclei of hypothalamus and transported to the posterior pituitary.

**Regulation of testicular function:** Testicular function is controlled by pituitary gonadotropins, LH and FSH, which are secreted in response to the gonadotropin releasing hormone (GnRH) secreted from the hypothalamus. LH controls testicular androgen production in Leydig cells, while FSH regulates spermatogenesis by acting via Sertoli cells. Furthermore, FSH also has an effect on the Leydig cells by stimulating the maturation of Leydig cells and also increasing the amount of LH receptors. LH secretion is inhibited by testosterone (T), estradiol (E2) and dihydrotestosterone through a negative feedback mechanism (Griffin & Wilson, 1998). The regulation of FSH secretion is not well understood.
Regulation of secretion of reproductive hormones in women: Pituitary FSH and LH regulate the ovarian function. The secretion of gonadotropins varies during the life span of women, i.e. the lowest levels are found in childhood and a circadian pattern of secretion is observed from prepuberty to the beginning of menopause. Gonadotropins regulate the follicle, which is the functional unit of the ovary. LH stimulates the androgen synthesis in the follicular theca cells, while FSH stimulates the maturation of the follicle and the conversion of androgens to estrogens in the granulosa cells. E2, progesterone (PROG), inhibin and follistatin secreted by follicle have a feedback effect on the release of gonadotropins. The ovarian biosynthesis of steroids is also regulated by insulin and insulin-like growth factors (Cataldo, 1997). The menstrual cycle consists of follicular, ovulatory and luteal phases. The median length of the cycle in healthy fertile women is 28 days with a range from 25 to 30 days. During the follicular phase FSH stimulates the maturation of the follicle and the secretion of estrogens and LH regulates the secretion of the androgens. In the ovulatory phase the increase of serum E2 levels at the hypothalamic-pituitary level triggers the ovulatory LH peak through a positive feedback resulting in ovulation. In the luteal phase the endocrine cells of the follicle are transformed into corpus luteum which secretes progesterones and E2. Progesterones and estrogens prepare the endometrium for the implantation of the fertilized egg. If implantation does not occur, the corpus luteum regresses and progesterone secretion drops dramatically causing menstrual bleeding. E2 is the most abundant estrogen in women. It is secreted in the ovary from A and T, and it stimulates the development of the uterus and characteristics for feminine appearance. E2 has a feedback effect on the hypothalamic pituitary unit and it is mainly bound to SHBG. (Carr, 1998) A and T are needed as precursors for production of estrone and E2. They are produced in the ovary and adrenal cortex. DHEA and dehydroepiandrosterone sulphate (DHEAS) are weak androgens and are mainly produced and secreted by the adrenal cortex being indicators of adrenal androgenesis. They are used as precursors when other steroids are synthesized. The synthesis of adrenal androgens is regulated by ACTH. Insulin-like growth factor I (IGF-I) and angiotensin may also contribute to the regulation of adrenal androgen synthesis. Although T is an important regulator of gonadotropin release in men, in women the serum levels of T are approximately one-tenth of those in men, and hyperandrogenemia does not inhibit the secretion of gonadotropins in women as effectively. Instead, estrogens and progesterone regulate the release of gonadotropins. However, if the serum T concentration in women exceeds the normal male level, the frequency of LH pulses decreases.

Sex hormone-binding globulin: In the circulation the most important bioactive sex steroid T and E2 are mainly bound to the plasma proteins SHBG and albumin. SHBG is a glycoprotein synthesized in the liver and has a high affinity and specificity to 17β-hydroxy steroids. It binds dihydrotestosterone and T with high affinity and E2 less effectively. About 1-2% of T and E2 is in the biologically active unbound form. In men about 60% of T is bound to SHBG and 40% to albumin, in women the distribution of bound form of T to SHBG/albumin is about 70%/30%. The serum SHBG concentration has an important effect on the bioavailability and peripheral conversion of T, dihydrotestosterone and E2. Pregnancy, hyperthyroidism, and estrogens increase, and corticosteroids, androgens, progestins, GH, insulin and IGF-I decrease serum SHBG concentration. In vitro studies have shown that androgens increase the SHBG synthesis in the hepatoma cell line. However, nutritional factors are even more important factors in the regulation of the SHBG production; weight is inversely related to the circulating SHBG level. The assumed mechanism is the effect of insulin and IGF-I, which suppresses the production of SHBG in the liver. Some medications may also affect SHBG levels, e.g. the use of hormonal contraceptives is associated with increased levels of SHBG. Altered serum SHBG concentrations have a clinical importance. Women with decreased levels of SHBG may have symptoms of hyperandrogenism (HA), which may be associated with polycystic ovary syndrome (PCOS). A low level of serum SHBG is also a marker for the development of type 2 diabetes and it can be used as a predictor of insulin resistance in women with PCOS (Cibula et al., 2002). Furthermore, decreased serum SHBG is also associated with coronary heart disease in women (Reinecke et al., 2002). Respectively, in men with epilepsy (MWE) a high concentration of serum SHBG may be associated with reduced bioactivity of serum androgens, which may manifest as diminished sexual function.

Polycystic ovary syndrome: PCOS was first described by Stein and Leventhal (Stein & Leventhal 1935) and it is the most common endocrine disorder in women of fertile age.
PCOS has an unknown etiology and it is assumed that there are several different pathways that may lead to the development of the syndrome. The prevalence of PCOS in the female population of reproductive age has been reported to be 4-10%. (Knochenhauer et al., 1998, Hopkinson et al., 1998, Guzick, 2004) However, the criteria for diagnosis have not been congruent in different studies. The diagnostic criteria for PCOS have been widely debated during the last decades and the consensus of the new diagnostic criteria was reached in 2003. The criteria for PCOS are (two out of three are needed for diagnosis) 1) oligo- and /or anovulation, 2) clinical (hirsutism, acne, androgenic alopecia) and/or biochemical signs of HA, 3) polycystic ovaries (PCO). PCO are diagnosed when 10 or more follicles of 2-8mm in diameter and increased and/or hyperechogenic ovarian stroma in ultrasonography or MRI are observed. (Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome 2004) PCO without the other features of PCOS is present in 10-23% of women who are not suffering from menstrual disorders or symptoms of HA (Borgfeldt & Andolf, 1999, Koivunen et al., 1999, Michelmore et al., 1999). Their prevalence is increased in younger women (Michelmore et al., 1999; Koivunen et al., 1999). PCO is not necessarily associated with HA or other signs of PCOS. However, 92% of women with idiopathic hirsutism and 87% of women with oligomenorrhea have PCO discovered in ultrasonography. The biochemical features of PCOS include increased serum levels of T, A, LH and insulin, and increased LH/FSH ratio. The serum concentration of SHBG and insulin-like growth factor binding protein 1 (IGFBP-1) are often decreased related to hyperinsulinemia in women with PCOS. The decreased levels of SHBG increase the bioavailability of T, and the androgen production in the ovaries increases due to the increased bioavailability of IGF-1. Anovulatory cycles interfere with the release of FSH, estrogen and progesterin and there is no normal cyclic secretion of these hormones in women with PCOS related an ovulation. Moreover, the other metabolic alterations that are often associated with PCOS, e.g. obesity, hyperinsulinemia, insulin resistance and dyslipidemia, may all predispose women with PCOS to cardiovascular diseases (Hopkinson et al., 1998; Guzick, 2004).

Epilepsy and reproductive function: Reproductive endocrine dysfunction is more common among epileptic patients than in the healthy population. Moreover, fertility is decreased in both men and women with epilepsy (Schupf & Ottman, 1996, Artama et al., 2004) which may be a consequence of epilepsy itself or the use of antiepileptic medication which may alter reproductive functions. Social factors may also contribute to reduced fertility in epileptic patients.

Effects of hormones on epilepsy: Hormones can affect seizure activity. In catamential epilepsy the frequency of seizures depends on the phase of the menstrual cycle as a consequence of altered levels of female sex steroids. It has been shown that estrogen is a proconvulsant, whereas PROG has anticonvulsant properties. Therefore, in catamential epilepsy the seizures usually occur in the end of the luteal phase when the levels of PROG rapidly decline. Consistent with this antiestrogenic clomiphene therapy and intermittent PROG therapy have decreased seizure frequency in women with catamenal epilepsy. Thyroid hormones also have effects on seizure activity. Thyreotoxicosis may predispose to seizures, and status epilepticus may be induced by thyroxine.

Effects of epilepsy on hormones: The first reports on the association between epilepsy and reproductive function were published in the 1950s suggesting that epilepsy is associated with hyposexuality. Thereafter several other reproductive disorders have been associated with epilepsy: irregular menstrual cycles, anovulation, hirsutism in women and decreased potency in men (Isojärvi et al., 1996). Abnormal reproductive function is also more prevalent in untreated epileptic patients than among the general population (Herzog et al., 2003). Furthermore, the serum concentrations of several hormones may be altered in epileptic patients, and increased secretion of pituitary hormones has been shown to be associated with seizures. The secretion of gonadal hormones can be affected by increased electrical activity associated with epilepsy. Electrical changes, which occur during the seizures and also during the interictal period, may interfere with the release of pituitary hormones and hence cause reproductive dysfunction. It has been shown that electrical discharges during both generalized and partial complex seizures increase the secretion of pituitary hormones. Furthermore, recurrent interictal paroxysmal discharges have also been suggested to interfere with the release of gonadotropins, which may be associated with dysfunction in the regulation of reproductive function. An association between the laterality of temporal lobe epilepsy and occurrence of certain reproductive endocrine disturbances has also been suggested. In Herzog's groups study left lateral discharges were followed by disturbances in LH secretion which affected the serum levels of T and DHEAS and the LH/FSH ratio and was associated with high prevalence of PCOS. On the other hand, right lateral discharges were associated with increased secretion of prolactin associated with hypergonadotrophic hypogonadism and disturbed sexual function. (Herzog et al., 2003).

Antiepileptic drugs and reproductive function: AEDs affect reproductive endocrine function in both men and women. Changes in reproductive hormone levels, decreased potency, and diminished sexual interest in men and menstrual disorders, PCOS and decreased fertility in women can be manifestations of the reproductive endocrine effects of AEDs. These disorders are frequently seen in association with certain AEDs. However, there is only limited information available on the effects of novel AEDs, e.g. OXC on reproductive endocrine function.

CARBAMAZEPINE AND OTHER LIVER ENZYME INDUCING

Antiepileptic drugs: CBZ and PHT induce the hepatic P450 enzyme system which results in an increased production of...
hepatic proteins such as SHBG and IGFBP-1 (Perucca et al., 2004). In men taking CBZ a progressive increase in serum SHBG levels and decrease in FAI ratio results in reduction of bioactive androgens and it has been suggested that these changes may lead to diminished sexual activity. Also low levels of DHEAS as well as disturbances in sperm motility and morphology have been reported in men taking CBZ (Rätyyä et al., 2001a, 2001b). Similarly, increases in serum levels of SHBG and decreases of bioactive androgen levels have been observed in patients taking PHT for epilepsy. PHT increases the serum concentrations of E2, which has been associated with sexual dysfunction in MWE. The effects of CBZ on reproductive function in WWE have been elucidated in several studies. These studies have consistently reported increased levels of SHBG and decreased levels of bioactive E2 and T in women taking CBZ for epilepsy. (Isojärvi 1996, Murialdo et al., 1998, Rätyyä et al., 2001) CBZ therapy has also been associated with low serum DHEAS levels (Murialdo et al. 1998). However, in previous studies the prevalence of menstrual disorders, PCO or PCOS in subjects on CBZ monotherapy has not been different from that of control subjects (Isojärvi et al., 2001, Murialdo et al., 1998, Bauer et al., 2000). PHT is associated with increased levels of SHBG, and decreased levels of DHEAS in WWE. Both PHT and CBZ reduce the efficacy of oral contraceptives by decreasing the bioavailability of ethinylestradiol and levonorgestrel.

**Oxcarbazepine:** Only few studies have been published on the effects of OXC on reproductive functions. OXC is considered a weaker inducer of the liver enzyme system than CBZ and its possible endocrine effects may be dose-related (Rätyyä et al., 2001b). A six-month follow-up study in men showed that after replacing CBZ with OXC the CBZ-induced alterations in the serum concentrations of reproductive endocrine hormones normalized during the 6 month follow-up. However, in another study in WWE, high doses of OXC monotherapy were associated with increased serum levels of T, gonadotropins and SHBG (Rätyyä et al., 2001b). The effects of OXC on reproductive function in WWE have not been studied previously. However, it is known that OXC decreases the bioavailability of ethinylestradiol and levonorgestrel of oral contraceptives and therefore reduces their efficacy (Fattore et al., 1999). Furthermore, exposure to OXC has been found to be associated with difficulties in achieving pregnancy in monkeys (Lockard et al., 2000).

**Valproate:** The effects of VPA on reproductive endocrine function have been widely studied and it is well known that the use of VPA is associated with reproductive disorders especially in women (Isojärvi et al., 2001, Isojärvi & Tapanainen, 2000, Rätyyä et al., 2001, Morrell et al., 2003). However, also MWE may have reproductive abnormalities related to VPA. Unlike other older AEDs VPA is not an inducer of the hepatic P450 enzyme system and in the earlier studies it was assumed not to have effects on reproductive endocrine function in men. Serum concentrations of LH, T, SHBG, and DHEAS have been reported to be normal (Geisler et al., 1997), while the concentrations of gonadotropins have been found to be low (Rätyyä et al., 2001b) and FAI ratio high in men on VPA therapy. Even though VPA has only a minor effect on the serum concentrations of reproductive hormones in men, case reports have associated it with infertility in MWE. VPA is also associated with changes in sperm quality in men (Sveberg et al., 2001). Furthermore, in rats and dogs VPA has been shown to be associated with testicular atrophy and reduced spermatogenesis (Sveberg Roste et al., 2001). In WWE VPA is often associated with HA, menstrual disorders, PCO (Morrell et al., 2003, Mikkonen et al., 2004), weight gain and hyperinsulinemia (Morrell et al., 2003). It has been suggested that obesity, hyperinsulinemia and low serum IGFBP-1 concentrations contribute to the development of HA associated with the use of VPA. However, HA and PCO are also found in lean women taking VPA for epilepsy. In the follow-up study these types of changes were reversible after discontinuation of VPA therapy (Isojärvi et al., 1998). Young age can increase the risk for these disorders. PCO and HA were especially common if VPA medication was started before 20 years of age. In young girls treated with VPA changes in androgen levels are already found before puberty. Increased levels of androgens were detected in all phases of puberty and they were associated with menstrual disorders. (Vainionpaa et al., 1999) Furthermore, after 5 year follow-up 60% of those girls whose VPA medication was continued had PCOS compared to 5.5% of those whose VPA medication had been discontinued or 8.3% of control subjects (Mikkonen et al., 2004b). The role of VPA as a contributor to the development of reproductive disorders in WWE has also been confirmed in studies evaluating the predictors of ovulatory failure and prevalence of PCOS (Morrell et al., 2002a, Betts et al., 2003). Interestingly, prolonged menstrual cycles and PCOS are also common in women with bipolar mood disorder on VPA monotherapy (O’Donovan et al., 2002). The pathogenesis of the VPA-related reproductive endocrine changes is still unknown. LH is a major inducer of androgen synthesis in the ovary, but its serum concentration is increased in only some patients with VPA related PCO. IGF-1 is known to potentiate the number of the LH-receptors in the ovary, causing stimulation of LH-induced androgen synthesis in the ovary. IGFBP-1 levels are decreased in VPA exposure and in hyperinsulinemia and the amount of bioactive IGF-1 increases inducing the ovarian steroid synthesis. Moreover, the bioavailability of androgens increases due to decreased serum levels of SHBG (Isojärvi et al., 1998). It has also been suggested that VPA has a direct effect on ovarian theca cells inducing the androgen biosynthesis; furthermore, in porcine ovarian follicular cells VPA exposure has inhibited T conversion to estrogen (Tauboll et al., 2003, Nelson-DeGrave et al., 2004).

**EPILEPSY AND REPRODUCTIVE DISORDERS**

**Type of epilepsy and reproductive disorders:** In the present study women with IGE had more often PCO, HA and PCOS than women with LRE or control women. This is congruent with a previously published study evaluating predictors of ovulatory failure in which women with IGE were at highest risk for anovulatory cycles, polycystic appearing ovaries, elevated body mass index (BMI) and HA (Morrell et al.,
2002a). However, LRE has also been observed to increase the risk of certain reproductive disorders, and the laterality of the epileptic focus may be important in this respect so that LRE with left sided focus has been suggested to be associated with PCOS, and LRE with right sided focus to be associated with hypothalamic amenorrhea and hypospermatogenesis (Herzog et al., 2003b).

Epilepsy itself may promote reproductive disorders by disturbing the hypothalamic regulation of secretion of pituitary hormones. Elevated levels of serum pituitary hormones have been measured after both partial and generalized seizure. Moreover, interictal electrical discharges can also predispose to increased secretion of pituitary hormones. The suggested increased prevalence of reproductive disorders in subjects with LRE is explained by the anatomy and physiology of the temporolimbic lobe. The epileptic focus may disturb the function of the temporolimbic hypothalamic axis, which regulates the release of reproductive hormones in an asymmetric manner. The electrical discharges during the seizures and in interictal period can spread from the temporal structures to the hypothalamus through direct connections and cause disturbances in the release of GnRH, which is situated and secreted asymmetrically in the hypothalamus. In a study in women with temporolimbic epilepsy the pulsatile secretion of LH and LH/FSH ratio was increased and concentrations of peripheral gland hormones T and E2 were also increased in women with left sided focus when compared to WWE with right sided focus (Herzog et al., 2003b). Similar results suggesting a different pattern of reproductive endocrine characteristics between patients with right or left sided epileptic focus have also been observed in other studies by the same investigators. However, in all these studies the patient population has been biased towards high seizure frequency and refractory epilepsy, and the patients have been referrals to a highly specialized tertiary care center. (Herzog et al., 2003a, 2003b) Interestingly, it has also been discussed whether reproductive disorders may promote seizures, since E2 is known to precipitate interictal epileptic brain wave activity and PROG is protective against seizures. Moreover, genetic factors in prenatal period can affect both the regulation of reproductive hormones and brain contributing to the development of epilepsy. The mechanism of IGE-related reproductive endocrine disorders is unclear, but mechanisms similar to the development of LRE-related reproductive endocrine disorders have been suggested. Electrical discharges during generalized seizures disturb the release of pituitary hormones; increased serum levels of LH and prolactin after generalized tonic clonic seizures have been reported in both men and women with epilepsy. The frequency of LH secretion pulses may also be altered in women with IGE. This has been shown in women with IGE and anovulatory cycles (Morrell et al., 2002a). Interictal generalized discharges may also disrupt the function of the hypothalamic-pituitary axis.

Predictors of reproductive disorders: In the present study the only factor that predicted the presence of PCO in WWE was the use of VPA and young age; these types of disorders were less common with increasing age. These results are consistent with previous reports (Isojärvi et al., 2001, Morrell et al., 2002a, Betts et al., 2003). Morrell et al. analyzed predictors of ovulatory failure in a cohort of WWE, and IGE and the use of VPA during the three previous years were independent factors that predicted ovulatory failure (Morrell et al., 2002a). In the present study the role of IGE was not detectable in regression analysis even though the prevalence of reproductive disorders was increased in women with IGE. This may be affected by the small number of patients in the analysis. Young age at the initiation of medication has not been analyzed as a possible factor to predict reproductive disorders in regression models in any of the previous studies. However, results from some studies have suggested that young age may predispose women to VPA-related reproductive endocrine disorders (Betts et al., 2003, Mikkonen et al., 2004b). Moreover, in a general population of healthy women PCO is more common in women under 36 years of age than in older women (Koivunen et al., 1999). In the present study increased body weight was not found to be a predictor of reproductive disorders, which is surprising since the role of obesity in development of reproductive disorders is well established (Morin-Papunen et al., 1998). In addition, the use of VPA can be associated with weight gain and obesity (Biton et al., 2001), which has been shown to be associated with reproductive disorders in WWE (Isojärvi et al., 2001). However, lean women on VPA therapy have also been shown to have high prevalence of reproductive endocrine disorders (Isojärvi et al., 2001). Despite the fact that the roles of epilepsy and the AED medication in contributing to the development of reproductive disorders in WWE has been widely discussed in the scientific literature during the last couple of decades, only a few previous studies have utilized a regression method in the analysis of factors contributing to the development of reproductive endocrine disorders in epileptic patients (Morrell et al., 2002a, Herzog et al., 2003a, Mikkonen et al., 2004a). The regression method is useful in this type of analysis, because it helps to identify factors that may contribute to the development of these type of disorders and enables the exclusion of the possible confounding effect of correlation between the factors possibly contributing to the development of the disorders. It is possible that in some of the previous studies correlation between the medication and epilepsy type has confounded the analysis and the results.

REPRODUCTIVE ENDOCRINE EFFECTS OF ANTIEPILEPTIC DRUGS

Carbamazepine: Women on CBZ did not differ from control women when prevalences of menstrual disorders, PCO, HA or PCOS were compared. In WWE CBZ was associated with reduced sperm concentration and high frequency of poorly motile sperm. The frequency of sperm with abnormal morphology was also higher in CBZ treated WWE than in the control men. CBZ treated men also had lower serum concentrations of DHEAS than control men. In WWE the effects of CBZ have been fairly extensively studied (Murialdo
et al., 1998). It is well established that CBZ induces the hepatic p450 enzyme system (Perucca et al., 2004) and increases the concentration of SHBG and thereby decreases the serum concentrations of bioactive androgens (Rätyyä et al., 2001b). The increase in serum SHBG concentration has been shown to be progressive. Low levels of serum DHEAS have also been reported in women taking CBZ for epilepsy. However, in previous studies the prevalence of reproductive disorders has not been different in women on CBZ from that of control women (Murialdo 1998, Bauer et al., 2000). The results of the present study were consistent with this. It has been discussed whether increased serum SHBG level may protect against the development of reproductive endocrine disorders in WWE by decreasing the levels of bioactive androgens (Isojärvi, 2002). On the other hand, long-term treatment with CBZ has been associated with menstrual disorders, which may be caused by diminished concentrations of bioactive E2 as demonstrated by the changes in the E2/SHBG ratio. The frequency of menstrual disorders and ovarian structure of women on CBZ did not differ from those of control women. However, in WWE taking CBZ together with VPA, the prevalence of HA and PCO was high. CBZ also increases the production of SHBG in men. This results in lower levels of bioactive androgens in target cells and decreased FAI (Rätyyä et al., 2001b). Low serum levels of DHEAS have also been reported in men on CBZ and this was also observed in the present study. It has previously been shown that CBZ does not change serum concentrations of T, but the level of bioactive free T, as calculated from serum T and SHBG concentrations, diminishes. This may be associated with sexual dysfunction, e.g. reduced potency and libido in men on long term CBZ treatment (Rätyyä et al., 2001b). The decreased levels of bioactive T are also assumed to have a negative impact on sperm quality, and, in addition, in an in vitro study CBZ was also shown to directly inhibit the formation of T in Leydig cells, which may affect spermatogenesis. In another in vitro study CBZ was associated with decreased sperm motility indicating a direct effect of CBZ on sperm quality. The serum levels of T in men on CBZ did not differ from those of men on OXC or VPA, or control men.

**Oxcarbazepine:** In women OXC was associated with higher prevalence of PCO and higher serum concentrations of A and DHEAS than in control women. In men OXC was associated with increased frequency of morphologically abnormal sperm when compared to control men. In women the effects of OXC on reproductive function have not been previously studied. OXC was not associated with reproductive endocrine abnormalities in girls during pubertal maturation (Rätyyä et al. 1999), and after a five-year follow-up the reproductive endocrine hormone levels of the same young women were normal. However, the prevalence of PCO was as high as 63% (5 of 8 women) in young women on OXC therapy in the follow-up study (Mikkonen et al., 2004b). The prevalence of PCO was increased in women on OXC compared with control women in the present study as well. In addition, the serum levels of A and DHEAS were higher in OXC treated WWE than in WWE on CBZ. This finding supports a hypothesis that OXC associated reproductive disorders may mainly be caused by induction of adrenal steroidogenesis, not the induction of the liver enzyme system. The serum SHBG concentrations of women on OXC did not differ from control women, which supports the hypothesis as well. OXC was also associated with low serum levels of T when compared to those of control women. Interestingly, serum T levels were similar in women taking low (<900 mg /d) or high (≥900 mg /d) doses of OXC. However, it is also possible that the reproductive endocrine disorders in OXC treated WWE are associated with epilepsy, and contrary to CBZ, the normal serum levels of SHBG and lack of effect on the bioactivity of androgens do not protect against the effects of increased serum androgens. There are only a few published studies on the effects of OXC on reproductive endocrine function in men (Rätyyä et al., 2001b, Mikkonen et al., 2004a, Artama et al., 2004). It has been assumed that OXC has less potential to interfere with the endocrine function than CBZ because it induces the liver p450 enzyme system only when taken in high doses. Furthermore, when CBZ was replaced with OXC the CBZ-induced alterations in the serum concentrations of reproductive endocrine hormones normalized in WWE. Normal serum levels of reproductive hormones have also been observed previously in young men on OXC (Mikkonen et al., 2004a) and the findings of the present study were consistent with this. The frequency of morphologically abnormal sperm was increased in men on all studied AEDs including OXC even though other parameters in sperm quality were normal in men on OXC. Interestingly, in a population based setting OXC was associated with lower birth rate when compared to untreated patients, while men on VPA or CBZ did not differ from untreated patients (Artama et al., 2004). However, it is also possible that in addition to OXC, epilepsy itself may interfere with spermatogenesis and reduce fertility in these patients.

**Valproate:** In women VPA was associated with elevated serum concentrations of T, and high prevalence of menstrual disorders, PCO and PCOS. In men VPA was associated with increased concentration of A, abnormalities in sperm quality and reduced testicular volume. The effects of VPA on women have been extensively studied (Isojärvi et al., 1998, Rätyyä et al., 1999, Bauer et al., 2000, Morrell et al., 2002a, Morrell et al., 2003, Betts et al., 2003). The role of VPA in the development of reproductive disorders (Isojärvi & Tapanainen, 2000, Morrell et al., 2002a, Tauboll et al., 2003, Mikkonen et al., 2004b) has been discussed and the effect of epilepsy has also been emphasized in recent years (Herzog & Schachter, 2001, Bauer et al., 2002). The methods used in reproductive endocrine studies on WWE have not been consistent throughout the studies. In some studies the information of the medication has not been complete, (Bauer et al., 2000) the data on previous medication has been incomplete and the use of imaging methods has varied in different studies (Bauer et al., 2000). Furthermore, the uniform definition for PCOS was not agreed upon until 2003 in Rotterdam, where international consensus of criteria was achieved. In previous studies in WWE, VPA has been associated with increased prevalence of menstrual disorders, PCO, HA and PCOS. VPA has also been associated with obesity and hyperinsulinemia (Isojärvi & Tapanainen, 2000, Isojärvi
et al., 2001, Morrell et al., 2003, Mikkonen et al., 2004b). The results of the present study were consistent with an association between VPA and reproductive endocrine disorders. Furthermore, in regression analysis the use of VPA was the most important factor in predicting the presence of HA, PCO and PCOS in WWE. Also in the study by Morrell et al. the use of VPA in the previous three years was one of the predictors of ovulatory failure (Morrell et al., 2002a).

Interestingly, VPA has also been shown to be associated with reproductive disorders in women with bipolar mood disorder (O’Donovan et al., 2002). It has been suggested that VPA-related HA, menstrual disorders, PCO and PCOS are associated with obesity and hyperinsulinemia (Isojärvi et al., 1998). However, HA and PCO have also been present in lean women without hyperinsulinemia (Isojärvi et al., 2001). Therefore, obesity can be included as one of several factors in this complicated syndrome associated with VPA. In fact, VPA may have a direct inhibitory effect on the ovaries and on steroid metabolism. VPA inhibits the conversion of T to estrogen, which may lead to development of HA in the ovarian microenvironment. This may disturb the follicular maturation and lead to development of polycystic appearance of the ovaries (Tauboll et al., 2003). In men VPA was associated with increased serum levels of A, which is consistent with results of previous studies in men on VPA therapy (Rättyä et al., 2001b, Mikkonen et al., 2004a). Unlike in the previous studies in which VPA was also associated with increased levels of serum DHEAS and T, and decreased serum levels of gonadotropins (Rättyä et al., 2001a), the serum concentrations of these hormones did not differ from those of the control men in the present study. There are only a few previous studies that have evaluated the possible effects of AEDs on male reproductive function by assessing the impact of the drugs on spermatogenesis (Sveberg et al., 2001, Sveberg Roste et al. 2003). In the present study VPA was associated with high frequency of poorly motile sperm. Interestingly, VPA was also associated with decreased motility of sperm in an in vitro study, which suggests a direct effect of VPA on semen quality. The normal motility of spermatozoa is dependent on adequate mitochondrial function, which may be affected by VPA. VPA was also associated with increased overall prevalence of sperm abnormalities and reduced testicular volume when compared to those of control men. Furthermore, men on VPA with abnormal sperm had smaller testicular volume than the control men, while men on VPA with normal sperm did not differ from controls when testicular volume was studied. In a previous study in young male subjects on VPA therapy their testicular volumes did not differ from those of control subjects. The sperm was not analyzed due to the young age of the participants. (Mikkonen et al., 2004a) Exposure to VPA has also been associated with testicular atrophy and reduced spermatogenesis in animals (Berner et al., 1999, Sveberg et al., 2001), but the mechanisms for VA-induced changes in testicular volume are still unclear. In this study VPA was also associated with abnormal sperm morphology. The effects of VPA on spermatogenesis may be explained by several factors. It has been suggested that VPA modifies the GABAergic neurotransmission (Arroyo, 2004) and thereby affects the secretion of gonadotropins, which are vital for normal spermatogenesis. The altered serum levels of gonadotropins could also be caused by increased serum levels of T by feedback mechanism in the regulation of the hypothalamic-pituitary-testicular axis. However, the serum levels of gonadotropins and T in men on VPA did not differ from those of control men in the present study.

**Epilepsy in population based setting:** The prevalence rates and incidence rates of epilepsy have been studied in many populations (Hauser & Hesdorffer, 2001, Forsgren, 2004, Oka et al., 2006).

**Prevalence of epilepsy:** The cumulative prevalence of epilepsy was 1.9% in NFBC 1966 which is relatively high when compared to worldwide prevalence of epilepsy (Forsgren, 2004). However, the results of the present study are in accordance with lifetime cumulative prevalence, which was 1-3% according to Hauser (Hauser, 1997). The difficulties in the comparison of prevalence and incidence rates in different studies are related to variation in definitions of seizure disorders and methods used in the different studies. For example, in the study evaluating the incidence of childhood epilepsies in NFBC 1966 only one seizure was needed for the diagnosis, therefore the cumulative prevalence was as high as 1.4%. In the present study the diagnostic criteria followed the ILAE recommendations and the diagnosis of childhood epilepsy was re-evaluated and reclassified. The prevalence of childhood epilepsies was congruent with the findings in other epidemiological studies. In population based studies conducted in Europe, the age adjusted prevalence rates in adults have been congruent, but these studies were focused on active epilepsy and cumulative prevalence rates have not been reported (Luengo et al., 2001, Oun et al. 2003). Compared to those studies, the prevalence of active epilepsy in NFBC is relatively high. This may be explained by the characteristics of the study population, e.g. the prevalence of unique hereditary diseases and disabilities has been relatively high in study population, which is caused by genetic isolation (Heikura et al., 2005).

**Epilepsy and fertility:** In the present study WWE did not overall differ from control women when fertility rates were compared. However, women affected by epilepsy during the adulthood were less fertile than WWE who had achieved remission before adulthood. Also, in MWE active epilepsy during adulthood was associated with decreased fertility, even though in overall comparison of the fertility rates of control men and MWE there were no differences. It is well established that epilepsy is associated with high prevalence of reproductive disorders, but there are only a few studies that have evaluated fertility in subjects with epilepsy in a population based setting (Artama et al. 2004, Artama et al. 2006). In previous studies subjects with epilepsy have been associated with lower marriage rate and fewer children than control subjects (Artama et al., 2004, Artama et al. 2006), but contradictory findings have also been presented (Olafsson et al., 1998). The reproductive endocrine disorders associated with epilepsy and antiepileptic medication are well established in
WWE (Morrell et al., 2002a, Herzog et al., 2003). Furthermore, the contributory role of these disorders to infertility is also well known in the general population (Kousta et al., 1999). Consistent with these findings, in the present study women who had active epilepsy and who were on antiepileptic medication during adulthood had reduced fertility when compared to women who had achieved remission before adulthood. Similarly, in a long-term follow-up study in young female subjects with epilepsy reproductive disorders were also common in subjects with active epilepsy, whereas the prevalence of reproductive disorders was similar to control subjects if antiepileptic medication was discontinued at adolescence (Mikkonen et al., 2004b). These findings support the view that active epilepsy and antiepileptic medication play an important role in the development of reproductive disorders and infertility in WWE. Interestingly, in the present study WWE who had achieved remission and the antiepileptic medication was discontinued before adulthood had a similar number of children to that of the control subjects. Also in MWE the number of children tended to be higher in if remission was achieved before adulthood than if the subjects had active epilepsy in the adulthood. It is established that epilepsy itself is associated with reproductive endocrine disorders also in men, but also the role of antiepileptic drugs in the development of these abnormalities is established. Furthermore, the effects of antiepileptic drugs on testicular structure, spermatogenesis and sperm quality (Yerby & McCoy, 1999, Sveberg Roste et al., 2003) may also contribute to decreased fertility associated with active epilepsy. However, it has been previously suggested that subjects with childhood epilepsies have fewer children than control subjects, eventhough they have achieved remission (Sillanpää et al., 2004). Regardless, it is important to note that the effect of epilepsy on fertility may be different depending on the activity of epilepsy later in life. In previously published studies MWE were more often single than control men (Wallace et al., 1998), which was also found in the present study. Men are more often stigmatized by epilepsy. This may affect social and economic status, which on the other hand may influence marital status (Morrell, 2002b, Sillanpää et al., 2004). In women the stigmatizing effect of epilepsy may be smaller, and the effect of epilepsy on marriage rate and fertility rates less evident. Interestingly, despite of lower socioeconomic position and lower marriage rate in MWE, the overall number of children was similar in MWE and control men, which is in discrepancy with previous studies (Sillanpää et al., 2004, Artama et al., 2004). However, consistent with what was seen in WWE, active epilepsy with antiepileptic medication during adulthood also reduced fertility in MWE. On the other hand, if remission was achieved before adulthood, MWE did not differ from control men with regard to fertility. This suggests that both active epilepsy with recurrent seizures and use of AEDs may contribute to reduced fertility in MWE and WWE. On the other hand, the design of the current study and the small number of patients in different subgroups with different epilepsy types or different AED regimens did not allow a reliable analysis of the impact of different epilepsy types or AEDs on reduced fertility.

Teratogenicity: The teratogenicity of anticonvulsant drugs shows that a distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself. Anticonvulsant drugs taken by pregnant women to prevent seizures are among the most common causes of potential harm to the fetus. Anticonvulsant drugs used frequently to prevent seizures, PBT, PHT, and CBZ were found to cause major malformations, microcephaly, growth retardation, and distinctive minor abnormalities of the face and fingers in infants exposed to them during pregnancy. Moreover, epilepsy is very often associated with CNS psychiatric disorders. The potential teratogenicity of AEDs is controversial and important. It is important because teratogenicity resulting from long-term drug treatment of millions of people throughout the world may have a profound effect even if the effect occurs in only a small percentage of cases. It is controversial because both epilepsy and AEDs are heterogeneous, and few epileptic patients are available for studies who are not receiving these drugs. Furthermore, patients with severe epilepsy, in whom genetic factors rather than drug factors may be of greater importance in the occurrence of fetal malformations, are often receiving multiple AEDs in high doses. In spite of these limitations, it appears-from whatever cause-that children born to mothers taking AEDs have an increased risk, perhaps twofold congenital malformations. PHT has been implicated in a specific syndrome called fetal hydantoin syndrome (skeletal, CNS, limb, and orofacial defects), although not all investigators are convinced of its existence and a similar syndrome has been attributed both to PBT and to CBZ. VPA has also been implicated in a specific malformation, spina bifida. It is estimated that a pregnant woman taking VPA has a 1–2% risk of having a child with spina bifida. In dealing with the clinical problem of a pregnant woman with epilepsy, most epileptologists agree that while it is important to minimize exposure to AEDs, both in numbers and dosages, it is also important not to allow maternal seizures to go unchecked. Topiramate has shown teratogenic effects in animals. The risk of the pregnant mother having a full blown seizure and having brain injury (hypoxia) are much higher than having a fetus with congenital defects. Thus, the risk to benefit ratio should be seriously considered. However, the pregnant mother taking AEDs should be closely monitored (Wagh et al., 2011; Gerlach and Krajewski, 2010).

DISCUSSION

The association of reproductive endocrine disorders with epilepsy has been extensively studied during the last decades. However, it is still uncertain whether these disorders are a consequence of epilepsy itself or antiepileptic medication or both. Adequate antiepileptic medication can help subjects with epilepsy to reach complete seizure control, but at the same time AED associated adverse effects may have a negative impact on quality of life of WWE. Epilepsy
during adulthood can have a strong influence on reproduction and fertility, and the antiepileptic treatment may also induce reproductive disorders (Herzog et al., 2003a, 2003b, Isojärvi et al., 2001, Bauer et al., 2000, Rättyä et al., 2001b, Bauer et al., 2002, Morrell et al., 2002a, Morrell et al., 2003, Betts et al., 2003, Mikkonen et al., 2004a, 2004b). Moreover, AEDs may have teratogenic effects during pregnancy (Barrett & Richens, 2003, Gailly et al., 2004, Artama et al., 2005), which may change the views of WWE on childbearing and potential pregnancy. In the present study the effects of AEDs and epilepsy on reproductive endocrine function were evaluated in MWE and WWE. All subjects included in studies I-III were of reproductive age and had no other illnesses than epilepsy, and women taking oral contraceptives were excluded. Moreover, all subjects had been taking the same antiepileptic medication for at least 6 months, a time period long enough to bring out the possible reproductive endocrine effects of the AEDs (Rättyä et al., 2001a). In study IV a population based setting was used to estimate the effect of epilepsy on fertility; the study population consisted of 12,600 subjects. More than 93% of subjects born in 1966 in Northern Finland were included in the study cohort, and the information was obtained from several sources to ensure reliability of the findings.

CONCLUSIONS

Epilepsy and antiepileptic medication contribute to the development of reproductive disorders in WWE. VPA medication, young age at the start of the medication, and IGE were found to increase the prevalence of reproductive endocrine disorders in WWE. The reproductive endocrine effects of OXC and CBZ are different in WWE. OXC is associated with increased prevalence of PCO and elevated serum levels of A and DHEAS whereas CBZ increases the serum SHBG concentrations and is associated with reduced bioactivity of sex steroids. CBZ, OXC and VPA are associated with high prevalence of sperm abnormalities in MWE. The testicular volume of VPA treated MWE with abnormal sperm quality is reduced. The possible association between VPA therapy and testicular atrophy calls for further studies. Active epilepsy with antiepileptic medication during adulthood reduces fertility in both men and women in a population based setting. If remission is achieved before adulthood, epileptic patients do not differ from control subjects with regard to fertility. Finally, while early AEDs may be potent anticonvulsants, many have dose-limiting toxicity and/or unacceptable side-effects, which prevent achieving adequate brain levels to completely control seizures. Finally, future efforts to discovery novel anticonvulsant drugs are likely to focus on mechanism-driven discovery of new drugs. New AEDs have broadened the therapeutic options in treating patients with refractory epilepsy and those who cannot tolerate conventional therapy. This will help for researcher to find out newer AEDs with lesser side effects. A further study to acquire more information concerning pharmacological activity is in progress.

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