Eur Arch Psychiatry Clin Neurosci (2004) 254 : 303–311 DOI 10.1007/s00406-004-0499-9

ORIGINAL PAPER

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# Impairment of inhibitory control of the hypothalamic pituitary adrenocortical system in epilepsy

Received: 13 August 2003 / Accepted: 20 February 2004

**Abstract** Excess comorbidity between depression and epilepsy proposes common pathophysiological patterns in both disorders. Neuroendocrine abnormalities were often observed in depression as well as in epilepsy. Lack of inhibitory control of the hypothalamic pituitary adrenocortical (HPA) system is a core feature of depression; main relay stations of this system are located in the amygdala and hippocampus, which are key regions for both disorders. Therefore we explored the feedback mechanism of the HPA system in epilepsy. In order to control for the impact of depression we focused on epilepsies without depression. We compared patients with epilepsy (subdivided by medication with or without hepatic enzyme inducing antiepileptic medication) with 16 healthy controls and 16 patients with unipolar major depression but without epilepsy. We observed a lack of inhibitory control of the HPA system in patients with epilepsy, also in the absence of enzyme inducing medication. An impact of the temporal lobe location of the epileptic focus could not be observed. Thus, epilepsies share with depression the deficiencies in the feedback mechanism of the HPA system, proposing common pathophysiological features of up to now unknown nature.

**Key words** epilepsy · depression · Dex/CRH test · HPA · cortisol · dexamethasone

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## Introduction

Alterations of the hypothalamus-pituitary-adrenocortical (HPA) system regulation are a constitutional element of depression (Dinan 2001; Holsboer 1999; Holsboer 1998; Plotsky et al. 1998). Levels of circulating cortisol and ACTH are increased due to a deficient inhibitory feedback system. It has been proposed that the resulting hypercortisolism is responsible for reduced neuronal outgrowth and plasticity with volume reductions in the hippocampus and cognitive deficits as one possible consequence (Sapolsky 2000; Sheline et al. 1996; McEwen et al. 1992; Sapolsky et al. 1986).

Several reasons argue for similar endocrinological abnormalities in epilepsy or subgroups of epilepsy:

(1) Diagnostic unspecifity of lack of inhibitory control of the HPA system and the involvement of hippocampus/amygdala: depression-like HPA dysregulations were observed in several other psychiatric disorders, e. g. in manic episodes (Schmider et al. 1995), schizophrenia (Lammers et al. 1995), in anxiety disorders (Schreiber et al. 1996), anorexia nervosa (Duclos et al. 1999) and during alcohol withdrawal (Hundt et al. 2001). Alterations were also observed in Alzheimer's disease (Rasmuson et al. 2001; Hatzinger et al. 1995) and neurological diseases like multiple sclerosis (Then Bergh et al. 2001; Kumpfel et al. 1999; Fassbender et al. 1998; Grasser et al. 1996). All these diseases have the involvement of the hippocampus and/or amygdala in common which are target regions for control of the HPA system and for the sequelae of HPA dysregulations:

Neurons including the corticotropin-releasing factor are particularly prominent in the central division of the extended amygdala (Heimer 2003), which reveals structural changes in depression (Drevets 2003; Frodl et al. 2002; Sheline et al. 2001; Drevets 2000) and temporal lobe epilepsy (Aliashkevich et al. 2003).

Furthermore the hippocampus is postulated to be

the major site of potentially deleterious actions of steroids (Sapolsky 2000; Sapolsky et al. 1986).

In this context it is remarkable that marked abnormalities of the hypothalamic pituitary gonadal (HPG) regulation and reproductive function have been reported in epilepsy patients (Bauer et al. 2002; Herzog 1989, 1999).

(2) Common pathophysiological features: Treatment-resistant depression and epilepsy can both be treated with vagus nerve stimulation (George et al. 2002; Schachter 2002; Cramer et al. 2001; Rush et al. 2000; George et al. 2000a, 2000b), what points to an imbalance between parasympathetic (vagal) and sympathetic nervous system activation in both disorders or subgroups of them. A particularly important structure in this context is the amygdala (Henry 2002), which receives large projections from the nervus vagus; the modulation of the activity of the amygdala might contribute to the therapeutic effect of vagus nerve stimulation (Henry 2002; George et al. 2000b, 2000c), which might include modulation of the CRH containing neurons in this area.

(3) HPA dysfunction due to repetitive or chronic stressful events: seizures, if occurring in a repetitive manner, are stressful events for the organism, which can cause lack of inhibitory control in the HPA system (Holsboer 2001; Kudielka et al. 1999; Checkley 1996; de Kloet 1995); thus HPA dysfunction might be induced in epileptic disorders independent of the localization of the focus.

Therefore we tested if HPA dysregulation can also be observed among patients with epilepsy (particularly TLE).

Several methods to evaluate the regulation of the HPA system have been used in the last few decades (e. g. the assessment of the inhibitory control of the HPA system after stimulation with dexamethasone, the so called dexamethasone suppression test). The currently most refined and sensitive neuroendocrine function test to explore the inhibitory feedback mechanism combines suppression by dexamethasone with subsequent stimulation with corticotropin releasing hormone (CRH) (so called Dex/CRH test). The hypersecretion of cortisol in response to first dexamethasone and subsequently CRH administration can be interpreted as a reduced feedback activity of the HPA system; ACTH concentrations may also be informative and mainly reflect the rate of change in the activity of the HPA system (Heuser et al. 1996). HPA dysregulation during depressive episodes, measured by the Dex/CRH test, was demonstrated by several authors (Rybakowski and Twardowska 1999; Heuser et al. 1994; Bardeleben and Holsboer 1989; Holsboer et al. 1987). Reduced inhibitory feedback control was also observed after repetitive or chronic exposure to stress (Vanitallie 2002; Miller and O'Callaghan 2002; McEwen 2001; McEwen 2000; Cacioppo et al. 1998; Checkley 1996; Sapolsky et al. 1986). Yet the application of the Dex/CRH test is complicated under simultaneous medication with hepatic enzyme inducing drugs, e. g. carbamazepine, which is also used as a mood stabilizer in the treatment of bipolar disorders and as an anticonvulsant (Zobel et al. 2001; Robertson et al. 1986; Holsboer et al. 1986). Other anticonvulsant drugs (oxcarbazepine, phenytoin and phenobarbital) are also known to have inductive effects on liver enzymes (French and Gidal 2000; Benedetti 2000; Tecoma 1999; Whysner et al. 1996; Volk et al. 1995) and thereby induce the degeneration of dexamethasone and decrease its suppressive power, resulting in blunted suppression of cortisol and ACTH.

Thus, we use the Dex/CRH test to examine 1) if epilepsy is associated with a reduced inhibitory feedback control of the HPA system even in absence of comorbid depression, indicating the limbic system to be a pathophysiological link between epilepsy and depression, and 2) if the HPA hyperactivity can also be observed in the absence of anticonvulsant drugs inducing the degeneration of dexamethasone.

## Material and methods

### Subjects

#### Patients with epilepsy

**Diagnosis and assessment.** All in-patients, consecutively admitted at the department of epileptology of the university of Bonn for diagnostic or therapeutic reasons between March 2001 and March 2002 were screened. Patients with acute or chronic medical conditions other than epilepsy were excluded. Classification of epilepsy and exclusion of patients with non-epileptic seizures was based on simultaneous video-EEG recordings of the semiology of the seizures as well as ictal brain activity. Additional deduction of EEG via deep brain electrodes was performed in some cases. Patients were enrolled in the study after obtaining written informed consent. Patients, who agreed to participate in the study, underwent a psychiatric diagnostic evaluation using a Structured Clinical Interview for DSM-IV (SKID) for diagnostic classification of psychopathological symptomatology administered by a senior psychiatrist.

**Sample of patients with epilepsy.** A total of 67 patients were enrolled in the final analysis (38 patients with temporal lobe epilepsy (TLE) (age 39.7 ± 10.3 years; 19 men, 19 women), 11 patients with an extratemporal focus (exF) (age 36.5 ± 10.5 years; 6 men, 5 women) and 18 patients with cryptogenic epilepsy (age 40.7 ± 9.4 years; 10 men, 8 women)) after ex post exclusion of patients who could not clearly be classified according to their epileptologic diagnosis or suffered from non-epileptic dissociative seizures, major psychiatric disorders or severe psychopathological symptoms (manifest depressive symptomatology, psychotic features). Thus, the remaining 67 patients in this study did not suffer from psychotic, affective or anxiety disorders (exception simple phobias) or drug/alcohol abuse or addiction. Duration of epilepsy and seizure frequency during the last month, respectively, were: 23.2 ± 13.4 years, 9.4 ± 11.0 in the TLE group; 17.0 ± 12.3 years, 14.6 ± 22.6 in the exF group and 18.6 ± 14.0 years, 8.2 ± 5.7 in the group with cryptogenic epilepsy.

**Anticonvulsant treatment.** All included patients with epilepsy were on a stable medication with antiepileptic drugs over several, but at least 4 weeks. A Dex/CRH test was administered shortly after admission before change of medication.

Overall 10 patients were treated with a monotherapy (TLE group: four with carbamazepine (CBZ), two with lamotrigine (LTG), one with phenytoin (PHT); exF group: one with LTG; group with cryptogenic epilepsy: one with CBZ, one with primidon (PRM)). The remaining 57 patients received a combination of two to four antiepileptic drugs,

comprising CBZ, oxcarbazepine (OXC), PHT, PRM, phenobarbital (PB), valproate (VPA), levetiracetam (LEV), topiramate (TPM), LTG, gabapentin (GBP), tiagabine (TGB) and vigabatrin (VBG) (Table 1). Mean daily dosages ± SD and mean plasma levels ± SD as available are depicted in Table 2.

In the TLE group, 8 patients were additionally treated with benzodiazepines (two with clonazepam (1 mg/d), 4 with clobazam (13.7 ± 4.8 mg/d), 2 with lorazepam (2.2 ± 1.1 mg/d); in the exF group was one patient additionally treated with 15 mg/d clobazam; in the group with cryptogenic epilepsy two patients were treated with clobazam 10 mg/d, one patient with clonazepam 0.5 mg/d.

Overall 57 patients were treated with drugs which are known to induce hepatic enzymes (PHT, PB, PRM, CBZ or OXC; 32 in the TLE group, 10 in the exF group and 15 in the group with cryptogenic epilepsy) (French and Gidal 2000; Benedetti 2000; Whysner et al. 1996; Volk et al. 1995). Ten patients received solely antiepileptic drugs without enzyme inducing potential.

**Table 1** Number of patients receiving mono- or combination therapy (2 to 4 drugs) in the three groups of patients with epilepsy (TLE, ExF, cryptogenic epilepsy)

| | TLE (n = 38) | exF (n = 11) | cryptogenic epilepsy (n = 18) |
|---|---|---|---|
| Monotherapy | | | |
| CBZ | 4 | – | 1 |
| LTG | 2 | 1 | – |
| PHT | 1 | – | – |
| PRM | – | – | 1 |
| Combination | | | |
| 2 drugs: CBZ, PHT, PB, PRM, VPA, LTG, TPM, LEV, GBP, VGB | 21 | 5 | 12 |
| 3 drugs: CBZ, OXC, PHT, PB, VPA, LTG, TPM, LEV, GBP, VGB, TGB | 9 | 5 | 3 |
| 4 drugs: CBZ, OXC, VPA, LTG, TPM, LEV | 1 | – | 1 |

Overall 27 patients were treated with antiepileptic drugs which are known to exert their antiepileptic action by GABAergic mechanisms (TGB, GBP, VGB, TPM, PB, PRM; 14 in the TLE group, 5 in the exF group and 8 in the group with cryptogenic epilepsy) (Sills 2003; Angehagen et al. 2003; Elger and Schmidt 1999; Davies 1995; Treiman 1903). Forty patients were treated with antiepileptic drugs that block neuronal ion channels and/or exert antagonistic action at the n-methyl-D-aspartate (NMDA) subtype of the glutamate receptor.

Patients receiving antidepressant drugs 1 month before conducting the Dex/CRH test were excluded from the start.

### Depressed patients without epilepsy

Patients with depression and without epilepsy were included in this study in order 1) to test the internal validity of the applied Dex/CRH test (by demonstrating the previously described patterns of hypersecretion compared to controls) and 2) to compare in an exploratory manner the level of hypersecretion between patients with epilepsy and patients with depression.

The group of depressed patients comprised 16 in-patients (8 men, 8 women; mean age 37.6 ± 9.1 years) referred to the Department of Psychiatry of the University of Bonn for treatment of major depression. These patients were selected from a larger sample by the criteria age and gender in order to attain comparability to the patients with epilepsy. All patients enrolled met the criteria for a major depression consistent with DSM-IV according to a SKID interview and clinical diagnosis. We selected patients with an antidepressant monotherapy with citalopram. About two thirds of the patients also received medication with lorazepam because of strong anxiety and restlessness. Patients with other medications influencing the central nervous system, particularly antipsychotics or mood stabilizers like carbamazepine, were not included. The Dex/CRH test was conducted shortly after admission and initiation of the antidepressive medication under stable conditions according to the protocol as described below. At this time point Dex/CRH results have been shown to be independent of the kind of antidepressive medication (Kunzel et al. 2003; Zobel et al. 2001).

### Healthy controls

The control group was included in this study a) to test if patients with epilepsy reveal a dysfunctional Dex/CRH test and b) to test internal validity of the Dex/CRH test by comparison with the patients with de-

**Table 2** Mean daily dosages (mg) ± SD and mean plasma levels (µg/ml) ± SD of antiepileptic medication in the three groups of patients with epilepsy (TLE, exF, cryptogenic epilepsy)

| | TLE (n = 38) | | | exF (n = 11) | | | Cryptogenic epilepsy (n = 18) | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | mean dosage/d (mg) ± SD | mean plasma level (µg/ml) ± SD | n | mean dosage/d (mg) ± SD | mean plasma level (µg/ml) ± SD | n | mean dosage/d (mg) ± SD | mean plasma level (µg/ml) ± SD |
| CBZ | 25 | 1212.0±525.4 | 10.2±5.1 | 6 | 1483.3±621.0 | 9.5±1.9 | 9 | 1560.0±669.3 | 11.1±7.6 |
| OXC | 0 | – | – | 0 | – | – | 2 | 1500.0±848.5 | 22.7±6.2 |
| PHT | 6 | 329.2±138.2 | 12.1±5.9 | 1 | 200.0 | 4.7 | 3 | 316.7±104.1 | 17.8±5.7 |
| PB | 2 | 125.0±35.4 | 17.1±6.0 | 2 | 125.0±35.4 | 15.7±7.9 | 1 | 200.0 | 22.7 |
| PRM | 2 | 1000.0±0 | 18.4±9.5 (PB) 11.4±0.4 (PRM) | 1 | 375.0 | 5.5 (PB) 5.6 (PRM) | 1 | 375.0 | 5.3 (PB) 5.8 (PRM) |
| VPA | 6 | 1766.7±720.2 | 51.1±16.2 | 3 | 1933.3±1504.4 | 37.3±22.0 | 3 | 2466.7±503.3 | 77.5±29.2 |
| LTG | 12 | 539.6±251.2 | 6.8±4.4 | 5 | 530.0±198.7 | 4.6±2.8 | 6 | 458.3±215.4 | 3.7±2.1 |
| TPM | 7 | 257.1±148.4 | 3.1±0.5 | 2 | 150.0±70.7 | 3.4±0.5 | 2 | 325.0±106.1 | 3.3±0.4 |
| LEV | 17 | 2294.1±1090.6 | * | 5 | 2800.0±1303.8 | * | 4 | 3250.0±288.7 | * |
| GBP | 2 | 1600.0±565.7 | * | 1 | 2400.0 | * | 0 | – | – |
| TGB | 0 | – | – | 0 | – | – | 2 | 37.5±3.5 | * |
| VGB | 1 | 250.0 | * | 0 | – | – | 2 | 2000.0±1414.2 | * |

* not available

pression. The group consisted of 16 healthy volunteers (8 men, 8 women; mean age 33.6 ± 10.2 years); these controls were matched according to age and gender to the patients with epilepsy. Controls were free of any medication.

### Dexamethasone/CRH test

#### Test protocol

A combined Dex/CRH test was performed in each individual shortly after admission to the hospital under stable conditions of all medication over several weeks. After pretreatment with an oral dose of 1.5 mg dexamethasone at 23.00 h five blood samples were drawn the next day at 15.00 h, 15.30 h, 15.45 h, 16.00 h and 16.15 h; 100 µg of human CRH was injected at 15.02 h after the first blood sample. Plasma cortisol and ACTH concentrations of the first sample reflect the suppressive effects of the dexamethasone administered the previous day, whereas cortisol and ACTH concentrations of the other samples show the additional effects of the CRH challenge.

#### Hormone assays

Plasma cortisol and ACTH concentrations were determined in the Department for Biochemistry of the University of Bonn observing standards previously described by Heuser et al. (Heuser et al. 1994, 1996). Commercially available radioimmunoassay (RIA) kits were used for cortisol measurements with a detection limit of 0.2 µg/dl plasma and intra- and interassay coefficients of variation of 8.1 % and 3.65 %, respectively. For analysis of the ACTH concentrations, an immunoradiometric assay without extraction was used. The detection limit was 5.0 pg/ml and the intra- and interassay coefficients of variation were 7.4 % and 5.55 %. Cortisol and ACTH analyses accuracy of the Department of Biochemistry was controlled by cross-laboratory validation studies.

Plasma dexamethasone concentrations were determined with tandem mass spectrometry (LC-MS/MS). To 100 µl of plasma in a glass tube, 50 µl internal standard dihydrotestosterone (c = 0.5 mg/l in methanol) was added and the analytes were extracted with 3 ml diethylether. After separation the organic phase was evaporated with a gentle stream of nitrogen in a waterbath set to 40 °C. The residue was taken up in 100 µl methanol and 5 µl was injected into the HPLC. Separation was achieved with a mobile phase MeOH/0.1 % formic acid 80:20 and a flow rate of 0.2 ml/min on a reversed phase C18-column 50*2 mm. Two MRM transitions 393.2/373.1 amu for dexamethasone and 291.2/255.3 amu for the internal standard were monitored in the positive-ion mode on an Sciex API 4000 triple-quadruple mass spectrometer operating with a turbo ionspray. Quantification was achieved by preparing standards in calf serum, which was spiked with a known concentration of dexamethasone (Merck, Darmstadt). The detection limit was 0.1 µg/l; intra- and interassay coefficients of variation were 2.6 % and 6 %, respectively (Huesgen et al. 2000).

### Statistical analyses

For testing the hypothesis of an HPA system disturbance in epilepsy even in absence of depressive symptomatology, in the first step we compared the whole group of patients with epilepsy with controls. Then patients with epilepsy were subtyped by GABAergic medication, medication with benzodiazepines and hepatic enzyme inducing medication. In a second step a one-way ANOVA with the between-subject factor group (controls (C), patients with epilepsy with (E_I+) and without (E_I–) enzyme inducing medication) was computed. Post hoc tests were performed using Scheffé procedure.

We also explored the effect of the temporal lobe localization of the focus by two factor ANOVA (factors: E_I+ versus E_I–; TLE+ versus TLE–).

In order to control the validity of the Dex/CRH test setting as applied in this study (internal validation), a) we compared the obtained cortisol measures to data given in the literature and b) we compared depressed patients and healthy controls by two-tailed t-tests for independent samples (quantitative variables: age, mean cortisol value, area under the curve (AUC) cortisol, mean ACTH value).

The study was conducted according to the regulations of the Federal Republic of Germany and the Declaration of Helsinki which includes approval by the local ethical committee.

## Results

### Hormonal response to the Dex/CRH test in depressed patients versus controls

For internal validation of the Dex/CRH test we compared the hormonal secretion of the depressed patients with the healthy controls. As expected we found a significantly higher hormonal (cortisol) secretion in the depressed patients compared with the controls (t-test for independent sample means: mean cortisol: $p = 0.00$, $df = 30$; AUC cortisol: $p = 0.00$, $df = 30$; mean ACTH: $p = 0.00$, $df = 30$) (Table 3). These results are in accordance with the results of previous studies. The amount of cortisol and ACTH secretion was comparable to previous findings in both groups (Zobel et al. 2001; Heuser et al. 1994, 1996; Holsboer-Trachsler et al. 1991; Bardeleben and Holsboer 1989). Thus our laboratory setting applying the Dex/CRH test produces valid results.

### Epilepsy patients in comparison to controls and depressed patients

Highly significant elevations of the cortisol reaction to Dex/CRH challenge were obtained for the whole group of 67 investigated patients with epilepsy (E) compared to controls (results for controls see Table 3, results for E: maximum cortisol 176.9 ± 70.3, $t = 8.6$, $df = 81$, $p = 0.00$; mean cortisol 135.5 ± 56.0, $t = -6.3$, $df = 81$, $p = 0.00$; AUC cortisol 10078.3 ± 4229.6, $t = 8.1$, $df = 81$, $p = 0.00$; maximum ACTH 45.2 ± 36.2, $t = 4.1$, $df = 81$, $p = 0.00$; mean ACTH 30.1 ± 2.4, $t = 8.3$, $df = 81$, $p = 0.00$).

**Table 3** Comparison of hormonal response to the Dex/CRH test in depressed patients and controls

| Variables | Means and SD | | Comparisons (t-test) | |
|---|---|---|---|---|
| | Depressed patients | Controls | t | p |
| Age (years) | 37.1 ± 8.8 | 33.6 ± 10.2 | 1.05 | 0.31 |
| mean Cortisol (ng/ml) | 96.2 ± 51.0 | 19.6 ± 16.3 | 5.72 | 0.00 |
| AUC Cortisol ((ng/ml) x min) | 7143.5 ± 4020.3 | 1446.6 ± 1212.4 | 5.42 | 0.00 |
| mean ACTH (pg/ml) | 16.7 ± 8.0 | 7.1 ± 3.5 | 4.39 | 0.00 |

Subtyping the patients with epilepsy by current GABAergic (E_GABA+; n = 27) (TGB, GBP, VGB, TPM, PB, PRM) vs non-GABAergic (E_GABA–; n = 40) anticonvulsant medication (CBZ, OXC, LTG, PHT, LEV, VPA) provided no significant differences between the two groups: maximum cortisol: T = 1.03, df = 42, p = 0.31; mean cortisol: T = 1.41, df = 43.7, p = 0.17; AUC cortisol: T = 1.43, df = 44.6, p = 0.16; maximum ACTH: T = 0.51, df = 65, p = 0.62; mean ACTH: T = 0.71; df = 65, p = 0.48.

We also compared the endocrinological reaction to the Dex/CRH test between patients with epilepsy, who received GABAergic medication and/or benzodiazepines (E_GABA/BZ+; n = 36) vs. those who did not (E_GABA/BZ–; n = 31). Again we did not observe any significant differences in the hormonal secretion following the Dex/CRH test: maximum cortisol: T = 0.66, df = 63.9, p = 0.51; mean cortisol: T = 1.10, df = 65, p = 0.28; AUC cortisol: T = 1.11, df = 65, p = 0.27; maximum ACTH: T = 1.26, df = 65, p = 0.21; mean ACTH: T = 1.45; df = 65, p = 0.15.

Patients with epilepsy were also split into those without (E_I–, n = 10) and those with (E_I+, n = 57) hepatic enzymes inducing medication (PHT, PB, PRM, CBZ or OXC) in order to control for putative differences in the suppressive effect of dexamethasone induced by interaction with different antiepileptic drugs. We observed the following results: maximum cortisol: T = –4.03, df = 65, p = 0.00; mean cortisol: T = –4.48, df = 65, p = 0.00; AUC cortisol: T = –4.55, df = 65, p = 0.00; maximum ACTH: T = –1.40, df = 65, p = 0.17; mean ACTH: T = –2.01; df = 65, p = 0.05. The significant differences between both groups warrant more detailed analysis. Both subgroups were different by age and sex and also by size.

In order to avoid interference by unequal size and differential patient characteristics in the E_I– and the E_I+ group, we selected 16 patients of the E_I+ group, comparable to the E_I– group according to age and gender and the epileptologic diagnosis. Mean values of the maximum, mean and AUC cortisol values, and the maximum and mean ACTH values were enhanced in both groups of epilepsy patients compared to controls (Table 4, Fig. 1). Analysis of variance for comparison (ANOVA) of these two patient groups and controls provided strong statistical support for an excess response of cortisol and ACTH to Dex/CRH among epilepsy patients (maximum cortisol: F = 37.32, df = 2, p = 0.00; mean cortisol: F = 35.45, df = 2, p = 0.00; AUC cortisol: F = 33.22, df = 2, p = 0.00; maximum ACTH: F = 6.26, df = 2, p = 0.00; mean ACTH: F = 9.93, df = 2, p = 0.00) proposing reduced inhibitory feedback in the epilepsy groups. The differences to controls were more pronounced for the cortisol than for the ACTH indicators.

These intergroup differences in the ANOVA were not due to medication with hepatic enzyme induction and subsequent accelerated degeneration of dexamethasone: Significant elevations of cortisol were also found for all three indicators in the E_I– group in comparison to controls (Scheffé test: maximum cortisol: p = 0.01; mean cortisol: p = 0.03; AUC cortisol: p = 0.04), whereas there was no significant difference between the E_I– group and a sample of patients with major depression (with identical sample size as the control group) (maximum cortisol: T = –1.45, df = 24, p = 0.16; mean cortisol: T = –1.30, df = 24, p = 0.21; AUC cortisol: T = –1.30, df = 24, p = 0.21; maximum ACTH: T = 0.69, df = 24, p = 0.49; mean ACTH: T = 0.48; df = 24, p = 0.64) although the cortisol and ACTH response levels were smaller among E_I– than among depressed patients (see Table 4). However, medication with the enzyme inducing antiepileptic drugs induced a substantial increase of the steroid response to the Dex/CRH challenge: the E_I+ group showed significantly higher cortisol levels than the E_I– group (Scheffé test: maximum cortisol: p = 0.00; mean cortisol: p = 0.01; AUC cortisol: p = 0.00).

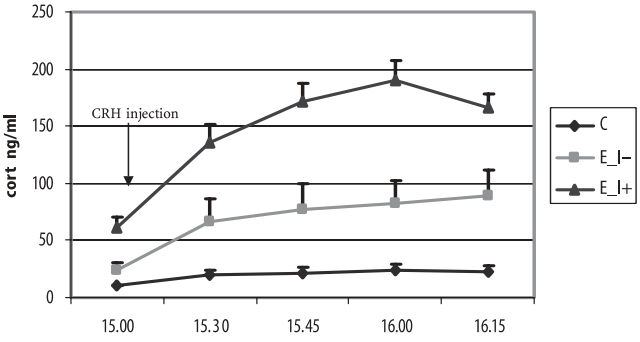


**Fig. 1** Cortisol profile in response to the Dex/CRH test (test procedure see methods) in patients with epilepsy with (E_I+) and without (E_I–) enzyme inducing medication and controls (C)

The differential results in different medication groups (E_I+, E_I–) of patients with epilepsy go together with different dexamethasone plasma concentrations (16 hours after oral administration, i. e. at 15.00 p.m the following day); the comparison between the E_I– (mean value = 0.9 ± 1.1 µg/l) and the E_I+ group (mean value = 0.00 ± 0.00 µg/l) revealed a significant difference (T = 2.81, df = 9.0, p = 0.02). On the other hand, dexamethasone plasma concentrations were nearly identical between the E_I– group and controls (mean value = 1.0 ± 0.5 µg/l) and also depressed patients (mean value = 1.1 ± 0.5) similar to previously described concentrations in depressed patients after recovery 16 hours after oral administration of 1,5 mg dexamethasone (Holsboer et al. 1986).

We further explored the impact of a focus in the temporal lobe on the reduced feedback mechanism (Table 4). The ANOVA in the sample of patients with epilepsy with AUC, maximum and mean cortisol as dependent and diagnostic group (TLE + versus TLE–) and enzyme inducing medication status (E_I+ versus E_I–) as well as their interaction as independent variables revealed only significant effects for enzyme inducing vs enzyme non-inducing anticonvulsants (maximum cortisol: F = 10.48, df = 1, p = 0.00; mean cortisol: F = 11.20, df = 1, p = 0.00; AUC cortisol: F = 10.75, df = 1, p = 0.00).

**Table 4** Mean cortisol and ACTH values (± SD) of patients with epilepsy (without (E_I–) and with (E_I+) enzyme inducing medication), depressed patients and controls

| Variable | Age (years) | maximum cortisol (ng/ml) | mean cortisol (ng/ml) | AUC Cortisol ((ng/ml) x min) | maximum ACTH (pg/ml) | mean ACTH (pg/ml) |
|---|---|---|---|---|---|---|
| E_I– | | | | | | |
| All (n = 10) | 37.4±10.2 | 97.9±78.9 | 67.7±56.4 | 4902.0±4232.6 | 32.1±51.2 | 19.8±24.6 |
| TLE+ (n = 6) | 39.2±11.0 | 96.8±93.5 | 67.6±68.6 | 4948.7±5197.4 | 38.4±67.0 | 21.8±32.0 |
| TLE– (n = 4) | 34.7±10.0 | 99.5±64.4 | 67.8±41.1 | 4831.9±2951.5 | 22.6±13.6 | 16.8±9.0 |
| E_I+ | | | | | | |
| All (n = 16) | 36.6±10.9 | 197.7±64.3 | 144.2±49.9 | 10649.5±3832.8 | 41.1±17.6 | 28.7±11.0 |
| TLE+ (n = 10) | 39.4±11.5 | 203.6±58.9 | 151.0±40.3 | 11128.5±3096.8 | 35.9±11.0 | 25.9±7.9 |
| TLE– (n = 6) | 32.0±8.6 | 188.0±77.2 | 134.8±65.9 | 9851.2±5058.2 | 49.7±23.8 | 33.6±14.4 |
| Depression (n = 16) | 37.1±8.8 | 148.3±87.4 | 96.2±51.0 | 7143.5±4020.3 | 23.1±12.2 | 16.7±8.0 |
| Controls (n = 16) | 33.6±10.2 | 24.9±22.4 | 19.6±16.3 | 1446.6±1212.4 | 8.0±4.7 | 7.1±3.5 |

## Discussion

This is the first study testing the feedback mechanism of the HPA system in epilepsy by stimulating the system with CRH after suppression by dexamethasone. It was shown that patients with epilepsy reveal reduced inhibitory control of the HPA system in the absence of depressive and anxiety disorders. A previous report by Robertson et al. using the dexamethasone suppression test (DST) pointed in a similar direction (Robertson et al. 1986); however in this report the effect of comorbid depression and enzyme inducing medication was difficult to disentangle. This observation of reduced negative feedback control in patients with epilepsy goes together with similar results in multiple sclerosis (Grasser et al. 1996) and stress related psychiatric disorders.

### The role of pharmacokinetics of dexamethasone

The interpretation of test results has to consider that hormonal secretion after Dex/CRH challenge might be influenced by dexamethasone kinetics. We observed major group differences for dexamethasone plasma levels 16 hours after application: the dexamethasone plasma levels 16 h after application were not detectable in the patients with epilepsy with hepatic enzyme inducing drugs and were higher in all other groups without being different between controls, depressive patients and patients with epilepsy without enzyme inducing drugs. As expected the degeneration of dexamethasone is accelerated by enzyme inducing drugs as proposed by Putignano et al. (Putignano et al. 1998).

However, dexamethasone plasma levels at a single time point might not be sufficient to identify pharmacokinetic influences. Moreover, the dexamethasone levels during the early night hours have previously been demonstrated to influence the outcome of the dexamethasone suppression test more than 17 hours after application (Holsboer et al. 1986). We were not able to measure plasma levels at the critical, early time point but the substantial differences 16 hours after application might also reflect differences 2 hours after application. Thus, it is likely that the hormonal response in the Dex/CRH test in epilepsy is increased by hepatic enzyme inducing drugs via accelerated degeneration of dexamethasone.

Dysfunctional HPA regulation was observed also in absence of enzyme inducing drugs (E_I–) with a baseline dexamethasone plasma level 16 h after application similar to controls and depressive patients. Although the excess cortisol and ACTH secretion after Dex/CRH challenge in the E_I– group was lower in magnitude than among depressed patients without epilepsy, there was no statistically significant difference. Since dexamethasone levels during the test in the E_I– group were grossly identical with dexamethasone levels in depressed patients (Holsboer et al. 1986), this difference reflects lack of inhibitory control of the HPA system in patients with epilepsy after control for enzyme inducing medication. Despite the significance of differences, the confidence intervals for the main measure cortisol AUC in epilepsy patients without catabolizing liver enzyme inducing drugs revealed major overlap with controls. Thus, this test cannot support the diagnosis of individual patients with epilepsy.

### Putative explanations

How to explain the lack of inhibitory control of the HPA system in epilepsy?

#### Localization of lesions

Lesions and cellular substrates in the limbic system, particularly hippocampus and amygdala, contribute to the generation and propagation of seizures (especially in TLE). These changes might also impact on those substructures controlling the HPA system which are located in the same region (e. g. neurons containing CRH in the amygdala, glucocorticoid receptors in the hippocampus) (Heimer 2003; Aliashkevich et al. 2003). However,

changes in the limbic system can not fully explain the lack of inhibitory control in patients with extratemporal epileptogenic foci. Yet, brain regions as the frontal cortex exert inhibition control on the amygdala; thus, extratemporal foci might induce changes in functions controlled by the amygdala as the HPA function. Propagation of epileptic discharge activity to temporo-mesial structures even from remote foci in extra-temporal epilepsy might also precipitate HPA disturbance.

### Common pathophysiological features with depression

Treatment refractory epilepsy as well as depression can be successfully treated with stimulation of the vagus nerve. The activation of the limbic structures as the amygdala is a putative mechanism of action. This communality between both disorders might point to common yet not identified amygdala related pathophysiological features. The preferential locations of CRH containing neurons in the extended amygdala is of interest in this context.

### Seizures as stressors

Seizures themselves increase cortisol secretion and thereby induce HPA alterations independent of the localization of the focus; for example it was shown that chronic electroconvulsive shock treatment increased secretion of hormones of the HPA system in rats (Young et al. 1990; Herman et al. 1989) and significant postictal elevations of serum cortisol (Takeshita et al. 1986) and ACTH secretion (Gallagher 1987) were observed in patients with epilepsy (for review see Pritchard 1991). A persistent hypersecretion of cortisol and ACTH can occur in vulnerable patients with the consequence of changes in the homeostasis of the HPA system (Holsboer 2001; Chrousos and Gold 1992). This mechanism operates in epilepsy independent of the localization of the focus and is also relevant for depression. The excess comorbidity between epilepsy and depression can also be explained by this mechanism (Harden 2002; Piazzini et al. 2001; Quiske et al. 2000; Altshuler et al. 1999; Trimble et al. 1997; Shukla et al. 1979).

## Common pathomechanisms?

Current evidence is unable to confirm that the loss of inhibitory control of the HPA regulation in depression and epilepsy is mediated by identical mechanisms. For example, vulnerability to HPA dysregulation has been proposed as one predisposing factor for depression; consequently, HPA hyperactivity as measured by Dex/CRH tests has also been reported for healthy subjects with a high familial risk for depression; excess cortisol secretion furthermore predicted future emergence of depression in these subjects in the follow-up period (as demonstrated by the Munich Vulnerability Study (Modell et al. 1998; Holsboer et al. 1995). Thus in affective disorders dysfunctional HPA regulation not only reflects the effect of depressive symptoms but also characterizes the elevated vulnerability to affective disorders in so far healthy subjects. On the other hand, premorbid dysfunctional HPA regulation is unlikely in epilepsy; instead, changes in multiple neuroendocrine systems (including the HPA) might occur as consequences of this disorder (e. g. the hypothalamic pituitary gonadal system (Bauer et al. 2002; Herzog 1989, 1999). Yet as HPA hyperactivity becomes manifest in patients with epilepsy, it may precipitate depressive symptomatology and account for the observed excess comorbidity of epilepsy and depression.

## Conclusion

Summarizing our results, we found a marked dysregulation of the HPA system in patients with epilepsy independent of the administered medication or the presence of comorbid symptoms of depression. While a direct affection of the temporal lobe does not seem to define the putative common pathophysiological basis of epilepsy and depression, other mechanisms like dysfunctional stress adaptation as well as indirect damage of limbic structures may have to be taken into account. Further studies in exploring the endocrinological relationship between epilepsy and depression are warranted: First, the lack of inhibitory control of the HPA system beyond TLE needs to be studied by subdividing the non-TLE foci according to their localization. Second, given similar results for the Dex/CRH test in epilepsy and depression an even more pronounced HPA dysfunction is to be expected for the combined diagnosis. Finally, time of onset of the lack of inhibitory control of the HPA system is essential to distinguish if HPA dysregulation is only a consequence of seizures or if it also characterizes the vulnerability to develop epilepsy (as it is the case for depression).

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