Overactivation of NMDA receptors in ammonia neurotoxicity: a target for neuroprotection?

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Ammonia is a neurotoxin implicated in an array of neurological disorders for which a collective term hyperammonemic encephalopathies (HA) was coined. Recent evidence strongly suggests that overactivation of NMDA receptors leading to excessive generation of the gaseous second messenger, nitric oxide (NO) and manifested by accumulation of cGMP in the extracellular space, i.e. incubation media (*in vitro*) [Monfort et al., Neurochem Int, 2002] or microdialysates of the affected brain structures (*in vivo*) [Hermenegildo et al., Hepatology, 2000; Hilgier et al., Eur J Pharmacol, 2003] is a critical step in the mechanism of acute ammonia neurotoxicity. In parallel, ammonia leads to the generation of oxygen radicals, which then interact with NO to form a highly toxic intermediate, peroxynitrite [Anderzhanova et al., Brain Res, 2003; Kosenko et al., Neurochem Res, 1995; Brain Res, 2000; Schliess et al., FASEB J, 2002]. Hence, suppression of the downstream effects of NMDA receptor overactivation appeared to be a plausible strategy to counteract the neurotoxic effects of ammonia. This report describes studies that addressed potential roles of two endogenous neuroprotective compounds, taurine and kynurenic acid (KYNA). Taurine is an antioxidant, cell membrane protectant and $GABA_A$ and glycine receptor agonist. When applied intracerebrally by microdialysis, taurine ameliorated ammonia-induced extracellular accumulation of free radicals and cGMP in the striatum [Hilgier et al., Eur J Pharmacol, 2003]. Co-infusion of taurine with a $GABA_A$ receptor antagonist bicucculine or a glycine receptor antagonist strychnine separately, partly restored the ammonia-induced cGMP synthesis, while simultaneous co-infusion of both antagonists or of a chloride channel antagonist picrotoxin almost completely offset the taurine block [Hilgier et al., Brain Res, 2005]. The results suggest that concerted stimulation of $GABA_A$ and glycine receptors is involved in the mechanism by which taurine limits the activation of the NMDA/ NO/cGMP pathway by ammonia in the striatum. Taurine also reduced ammonia-induced dopamine oxidation to DOPAC [Anderzhanova et al., Brain Res, 2003]. *In vitro*, taurine ameliorated ammonia-induced cell swelling in cerebral slices, and the effect, likewise, was abolished by a $GABA_A$ receptor antagonist [Zielińska et al., Neurochem Int, 2003]. Ammonia releases taurine from astrocytes *in vivo* [Zielińska et al., Neurochem Res, 2002] and *in vitro* [Zielińska et al., Neuroscience, 1999], which may promote its receptor-mediated interaction with ammonia-affected neurons. KYNA is an antagonist of NMDA receptor with a high affinity for its glycine site, whose inactivation by a synthetic antagonist abolished ammonia-induced cGMP accumulation [Hilgier et al., Brain Res, 2004]. Hyperammonemia in a hepatotoxicity (thioacetamide) model evoked stage-dependent changes in KYNA synthesis in the brain which showed inverse correlation with the neurological and metabolic manifestations of HA [Saran et al., J Neurosci Res, 2004]. As inferred from *in vitro* studies, this response involved both astrocytes and neurons [Wejksza et al., Neurotoxicology, 2006]. The results support the notion that manipulation of intracerebral content and/or distribution of taurine and/or KYNA may be considered in future therapy of acute HA.

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Treatment of drug-resistant epilepsy – clinical suggestions

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Almost one third of patients with epilepsy suffer from uncontrolled seizures despite state-of-the-art medical treatment [Kwan et al., N Engl J Med, 2000; Sander et al., J Neurol Neurosurg Psychiatry, 2004]. The reason of this resistance remains unknown. This is unclear why some patients with epilepsy can achieve satisfactory control of the disease with medication while others with seemingly identical symptoms and seizure types become drug resistant.

Currently two major neurobiological theories try to explain the intractability of epilepsy. The first puts forward that this can be attributed to the removal of antiepileptic drugs (AEDs) from the epileptogenic tissue by an excessive activity of multidrug transporters, while the second assumes the reduced drug-target sensitivity in epileptogenic brain tissue. According to clinical observation, drug resistance may emerge or remit during the course of epilepsy and its treatment, but in most patients it seems to be continuous. There is a known correlation between pharmacoresistance, features of seizures and epilepsy syndrome and structural brain lesions. In spite of different definitions of drug-resistance, most of experts would agree that epilepsy can be classified as drug-resistant (pharmacoresistant) whenever patients do not become seizure-free for twelve months of long-term adequate treatment with several suitable AEDs at maximal tolerated doses [Schmidt et al., Epilepsia, 2005]. The National Association of Epilepsy Centers has considered epilepsy as pharmacoresistant when seizures do not come under control after 9 months of treatment under the care of a neurologist. Berg et al. [Neurology, 2001] defined pharmacoresistant epilepsy in children as failure of two or more drugs to prevent one or more seizures per month over 18-month period. Modern strategy for treatment of epilepsy suggests a monotherapy with the first line AEDs. For patients, who do not respond to this therapy, sequential monotherapy, one-and-half therapy or full dose add-on therapy have to be introduced [Schmidt, 6th ECE, Vienna, 2004].

Medication with newer AEDs does not seem to prevent or to reverse drug resistance in most patients. Fortunately, some of them have modest reduction of seizures after add-on therapy with novel drugs and a few seem to be seizure free. Perucca [Epilepsia, 2005] reports that up to one third of patients refractory to the first AED respond to monotherapy with the second AED. Few patients refractory to two sequential AEDs respond to a third drug or to drug combination. There are no evidences that AED combinations offer advantages over sequential monotherapy particularly in the early stages of epilepsy. Clinical studies performed up to date on this issue have some limitations. Usually, small sample size and sequential designs do not allow to differentiate between effects of treatment and effects of time. It is also difficult to compare adequately specific AED combinations because not all AED combinations are equal. It is also unclear whether early use of AED combinations improves long-term prognosis of epilepsy [Perucca, Epilepsia, 2005].

Stephen and Brodie [Seizure, 2002] reported the audit of their clinical practice comprising intractable patients with epilepsy and they identified ten most effective two-AED combinations that were associated with seizure freedom for over one year. These clinically favorable two-AED combinations were compared with the results from maximal electroshock test (MES) in experimental studies on animals performed by Łuszczki et al. [Epilepsia, 2005]. Most of combinations phenobarbital + phenytoin (PB + PHT), carbamazepine + valproate (CBZ + VPA), CBZ + PHT, CBZ + topiramate (TPM), CBZ + gabapentin (GBP), lamotrigine (LTG) + TPM, LTG + VPA) showed additivity or synergy in interaction MES test, while few, clinically approved combinations, CBZ + vigabatrin (VGB) or CBZ + LTG, showed antagonism.

To illustrate the above-mentioned therapeutic problem, the treatment results of patients with epilepsy who sought assistance of a neurologist for the first time have been analyzed over the period of one year (September 2004–September 2005). The group consisted of 80 patients (males – 32, females – 48) from 17 to 78 years old (mean: 64.5 yrs) who were treated with monotherapy (50 patients), sequential monotherapy (9 patients), or with polytherapy (21 patients).

The patients from the last group (males – 8, females – 13) from 18 to 62 years old (mean: 35.5 yrs) were suffering from epileptic seizures for a period from 1 to 22 years (mean 15.2 yrs). They have presented complex partial seizures (5 patients), complex partial seizures with secondary generalization (12 patients) and generalized tonic-clonic seizures (4 patients). Seven patients from this group had cryptogenic epilepsy, 9 – symptomatic epilepsy and 5 – idiopathic epilepsy. Sixteen of them needed medication with a combination of 2 AEDs while 5 patients were administered combinations of 3 AEDs. The results of polypharmacotherapy with different AED combinations were as follows:
1) 5 patients were seizure free – CBZ + TPM (3 patients), VPA + TPM (2 patients)
2) 7 patients had seizure reduction over 50% – CBZ + TPM (2 patients), VPA + TPM (2 patients), VPA + PHT (1 patient), oxcarbazepine (OXC) + TPM (1 patient), VPA + LTG + TPM (1 patient)
3) 7 patients had seizure reduction below 50% – VPA + OXC (1 patient), VPA + GBT (1 patient), PHT + LTG (1 patient), VPA + LTG + PHT (1 patient), VPA + LTG + tiagabine (TG; 1patient), VPA + TPM + VGB (1 patient), PHT + PB + TG (1 patient)
4) 2 patients presented increased number of seizures – CBZ + VGB (1 patient), CBZ + LTG (1 patient).

Conclusions:

1) One of four patients with epilepsy from the analyzed group suffered from refractory or pharmacoresistant epilepsy. Their medication required combinations of two or more AEDs.
2) Sequential monotherapy or suitable AED combination based on the mechanism of their action allow for better control of epilepsy, frequently with lower doses of AEDs.
3) CBZ + VGB and CBZ + LTG combinations, which in the MES test in mice showed antagonism, also increased seizure frequency in epileptic patients. Although the number of patients was very limited, a correlation between experimental results and clinical data should be considered. This emphasizes the importance of pharmacological experimental studies for more effective treatment of epilepsy.

Cognitive deficits in epilepsy

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Abstract not submitted.

Antiepileptic drugs and neuroprotection

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Increasing evidence indicates that epilepsy can induce neuronal loss in the brain. Neurodegeneration may affect both neurons and glial cells [Leker et al., Brain Res Rev, 2003]. Other frequent reasons of central nervous system (CNS) destruction are traumatic brain injury and ischemia/hypoxia. In most experimental settings, neuronal damage occurs in the hippocampus (pyramidal neuronal loss in the CA1 and CA3 re-

gions). The type of damage is often similar to the histological picture observed in individuals with temporal lobe epilepsy intractable with conventional antiepileptic drugs (AEDs) [Sutula, Epilepsy Res, 2002]. Strategies leading to prevention, salvage, recovery or regeneration are referred to as neuroprotective [Sutula, Epilepsy Res, 2002].

Both seizures and neurodegeneration are usually triggered by the increased levels of the brain glutamate and are associated with:

– Na^+ and Ca^{2+} cation inward current
– Induction of inflammation
– Free radical production
– Increased cell catabolism, and finally
– Cell death by apoptotic (slow) or necrotic (fast) mechanism [Pitkänen, Epilepsy Res, 2002].

It is believed that excitation in the CNS is a result of imbalance between excitatory and inhibitory amino acids. Similarly, prevalence of proinflammatory cytokines may shift the balance towards apoptotic reactions [Vajda, J Clin Neurosci, 2002]. Therefore, options of neuroprotection are heterogeneous and include:

1. Glutamate antagonists
2. Na^+ and Ca^{2+} channel blockers
3. Neurotrophic factors
4. Free radical scavengers/antioxidants
5. Apoptosis-related protease inhibitors [Pitkänen, Epilepsy Res, 2002].

Neurons can display many different kinds of ionotropic and metabotropic glutamate receptors on their surface. Activation of ionotropic N-methyl-D-aspartate (NMDA) receptors leads to greater permeability of the cell membrane to Na^+ and Ca^{2+} cations. Channels linked to alpha-amino-3-hydroxy-5-methyl-isoxazolepropionate (AMPA) receptors are mainly permeable to Na^+ ions. However, the inward Ca^{2+} current may be observed in a specific configuration of AMPA receptors. Na^+ cations depolarize the cell membrane, while Ca^{2+} ions entry starts a chain of reactions involving catabolic enzyme and free radical production that eventually leads to neuronal death [Leker et al., Brain Res Rev, 2003; Löscher et al., Epilepsy Res, 2002].

In experimental models, seizure activity is significantly related to neurodegeneration. Not only status epilepticus or repeated seizures, but also a single seizure or interictal discharges may lead to cell death [Duncan, Epilepsy Res, 2002]. In the model of amygdala-kindled rats, neuronal density in the hilus of dentate gyrus was inversely proportional to the number of seizures [Sutula, Epilepsy Res, 2002]. A hypothesis exists that neurodegeneration of inhibitory cells in some neural circuits may be involved in the chain of epileptogenesis. The decreased GABAergic neurotransmission is one of seizure consequences. It may lead to the decreased anticonvulsive effectiveness of barbiturates (B) and benzodiazepines (BDA) in animal models of epilepsy [Czuczwar et al., Epilepsia, 1982].

Among the most promising candidates for neural protection are AEDs. Their mechanism of action includes the following:

1. Limitation of sustained repetitive firing (*via* Na^+ channel blockade)
2. Enhancement of GABA-mediated inhibition
3. Attenuation of activity of voltage-sensitive Ca^{2+} channels
4. Decrements in glutamate-mediated excitation [Löscher et al., Epilepsy Res, 2002].

The ideal AED should prevent the early and late phases of neurodegeneration, inhibit reorganization of neural network (epileptogenesis), and positively modify epilepsy progression [Pitkänen, Epilepsy Res, 2002]. It should be underlined, however, that there is an undoubted though not complete correlation between neurodegeneration, epileptogenesis and disease modification [Löscher et al., Epilepsy Res, 2002].

Theoretical basis of neuroprotection provided by AEDs is associated with their molecular targets. Several AEDs exhibit antiglutamatergic effects. Felbamate (FBM) is an antagonist of NMDA receptors, while phenobarbital (PB), topiramate (TPM) and talampanel (TLP) block AMPA receptors. Diphenylhydantoin (DPH), carbamazepine (CBZ), valproate (VPA), lamotrigine (LTG), gabapentin (GBP), zonisamide (ZNS), FBM and TPM belong to voltage-dependent Na^+ channel blockers. Levetiracetam (LVT), LTG, GBP, FBM and TPM can block Ca^{2+} channels. B and BDA have their recognition sites within the $GABA_A$ receptor complex. The group of positive allosteric modulators of $GABA_A$ receptor includes FBM, TPM and ZNS. Metabolism of GABA is inhibited by vigabatrin (VGB) and GBP. Tiagabine (TGB) attenuates re-uptake of GABA from the synaptic cleft. Finally, VPA can inhibit some apoptotic proteases [Vajda, J Clin Neurosci, 2002]. Since TPM and FBM have 4–5 equivalent mechanisms of action, the two drugs may be considered in terms of so-called functional polytherapy.

Neuroprotection seems sensible not only in the early phases of CNS injury, but also in later phases of neural plasticity. At the stage of disease modification, neuroprotective agents may inhibit both progression of cognitive impairment and development of drug-resistant seizures. Therefore, AEDs may be considered as the first-line neuroprotective factors. The second-line agents include antioxidants, nitric oxide synthase inhibitors and caspase inhibitors [Pitkänen, Epilepsy Res, 2002; Temkin, Epilepsia, 2001].

In ischemic and seizure models, the following AEDs exhibited significant neuroprotective action: BDA, PB, CBZ, DPH, VPA, FBM, GBP, LTG, TGB, TPM and VGB [Pitkänen, Epilepsy Res, 2002; Trojnar et al., Pol J Pharmacol, 2002]. It should be underlined, however, that a majority of AEDs may induce apoptosis in the CNS during prenatal and early postnatal life. In the light of those data, it seems interesting that TPM induces apoptotic processes only at relatively high doses, several times exceeding its 50% effective dose (ED_{50}) [Glier et al., Exp Neurol, 2004]. Furthermore, under experimental conditions, epileptogenesis was attenuated only by DZP, PB and TPM. DZP, FBM and TPM positively modified seizure progress [Leker et al., Brain Res, 2003; Pitkänen, Epilepsy Res, 2002].

Unfortunately, there is still no evidence that AEDs have significant neuroprotective, antiepileptogenic or disease-modifying properties in clinical conditions [Leker et al., Brain Res, 2003; Löscher et al., Epilepsy Res, 2002; Temkin, Epilepsia, 2001].

Experimental clues for the treatment of drug-resistant epilepsy

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Rational polytherapy may be recommended in patients whose seizures are poorly controlled with a single antiepileptic drug (AED). Approximately 30% of epileptic patients do not sufficiently respond to monotherapy and combinations of AEDs have to be considered in order to stop or at least reduce seizure frequency.

Some combinations of AEDs have been already evaluated in clinical conditions [Stephen et al., Seizure, 2002]. Nevertheless, there are 190 diverse two-drug combinations with 20 AEDs and, to be true, the last decade has been associated with the introduction of a considerable number of newer AEDs. All new drug combinations may be quite promptly tested experimentally and mainly those showing synergy in terms of anticonvulsant effects and antagonism as regards adverse activity, could be recommended for further clinical evaluation.

Isobolography is the major approach allowing to detect a precise nature of interactions between AEDs as supra-additivity (synergy), additivity, and subadditivity (antagonism). The results presented below have been calculated by isobolography in mice.

The distinct synergistic interactions were associated with combinations of gabapentin with carbamazepine (CBZ), oxcarbazepine, valproate (VPA), phenytoin (PHT), phenobarbital (PB), and lamotrigine in the maximal electroshock test (MES) in mice. Pharmacokinetic events accompanied the last two combinations since plasma gabapentin concentration was increased. No adverse effects (in terms of motor coordination and long-term memory) were evident [Borowicz et al., Epilepsia, 2002; Łuszczki et al., Eur J Pharmacol, 2005]. Co-administration of oxcarbazepine with other AEDs (PB, CBZ, and VPA), resulted in mainly additive interactions. Also, additivity was found in the chimney test (motor coordination). However, there was a clear-cut antagonism between oxcarbazepine and PHT at the fixed ratio combination of 1:1 (based upon their ED_{50} values) and additivity was observed in the chimney test [Łuszczki et al., Epilepsia, 2003a]. Tiagabine in combinations with PHT, CBZ, VPA, PB, lamotrigine, topiramate or felbamate led to additivity. Only its co-administration with VPA resulted in synergy against MES. This synergy, however, was accompanied by a considerable increase in the plasma and brain VPA concentrations [Łuszczki et al., Pharmacol Biochem Behav, 2003]. On the other hand,

a synergy evident for tiagabine and gabapentin against MES was not associated with pharmacokinetic events and generally, was free of adverse effects [Łuszczki et al., Neuropsychopharmacol, 2003]. Lamotrigine when combined with conventional AEDs (especially VPA) or topiramate showed synergy in the MES test in mice and antagonism in the chimney test, with no pharmacokinetic interactions [Łuszczki et al., Epilepsia, 2003b]. In contrast, a distinct antagonism between lamotrigine and CBZ was noted and followed by additivity in the chimney test, which makes this combination very unfavorable [Łuszczki et al., Epilepsia, 2003b]. One of the studies tested the interactions between some newer AEDs against MES. It is evident that some combined treatments, for instance topiramate + felbamate (synergy against MES and antagonism in the chimney test) and topiramate + oxcarbazepine (supra-additivity against MES and additivity in the chimney test) might be recommended for clinical evaluation. In contrast, combinations of oxcarbazepine + lamotrigine (antagonism against MES and synergy in the chimney test) and oxcarbazepine + felbamate (additivity against MES and synergy in the chimney test) are not expected to provide a sufficient protection in epileptic patients [Łuszczki et al., Epilepsia, 2004]. Finally, very recent data indicate that of numerous combinations of levetiracetam with conventional and newer AEDs, only these with CBZ, oxcarbazepine and topiramate were synergistic against MES. Pharmacokinetic interactions were excluded [Łuszczki et al., Epilepsia, 2006]. Finally, an assessment of drug interactions in the pentetrazole test (a model of myoclonic seizures) revealed that there was a synergy between vigabatrin and PB [Łuszczki et al., Neuropsychopharmacology, 2005] or vigabatrin and tiagabine (unpublished data).

Bearing in mind all limitations of employing data from experimental models of epilepsy in clinical practice, clinical trials are expected to verify the experimental results. However, it seems rational to recommend only beneficial AED combinations, selected preclinically, for further clinical testing.

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Pathomechanism of psychiatric abnormalities in patients with epilepsy

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Most of the data regarding neuroanatomic changes occurring in depression are connected with a decrease in the hippocampal volume. It correlates with the duration of depression, particularly in untreated cases [Frodl et al., Am J Psychiat, 2002]. Abnormalities in the brain structure, like reduction of the total brain volume, increased volume of brain ventricles and wide sulci as well as abnormalities of the temporal lobe are characteristic of schizophrenia. A majority of trials showed a decrease in the amygdaloid body in patients with schizophrenia [Keshavan et al., Schizophr Res, 2002]. Both structures are crucial to the development of refractory epilepsy as more than 70% of the patients demonstrate psychiatric abnormalities in the course of epilepsy.

Abnormalities at the cellular level seem to combine mechanisms implicated in refractory epilepsy and psychiatric disorders, namely an inhibition of cell proliferation, enhancement of apoptosis, decrease in the number and length of dendrites in CA3 hippocampal field [Frodl et al., Am J Psychiat, 2002]. Stress factors in predisposed patients may cause a decreased expression of neurotrophic hormone (BDNF – brain-derived neurotrophic factor) in the central nervous system, atrophy of the hippocampal cells and decline of neurogenesis in this structure, which may be asso-

ciated with occurrence of depressive symptoms [Smith et al., J Neurosci, 1995]. This is also probably responsible for depression in patients with drug refractory epilepsy in case of uni- or bilateral hippocampal sclerosis [Nibuya et al., J Neurosci, 1995].

Another interesting hypothesis explaining the problem of psychiatric disorders in patients with epilepsy is the kindling theory. The kindling model is based on long-term neuronal changes, with synaptic flexibility playing a crucial role. From neurophysiological point of view, kindling creates simultaneously two types of changes, i.e.: local epileptiform changes demonstrated by seizures and pathological activity in EEG, (widespread changes in neuronal plasticity) leading to long-term electrophysiological, neurochemical and behavioral alterations [Moore, Seizure, 1997; Trimble, Epileptologia, 2001].

Protracted and long-term changes in neural activity of the amygdala nucleus and hippocampal formation have been confirmed by altered behavioral responses during interseizure period observed in animal models. This can be explained by neurophysiological mechanisms involving extended cortical or subcortical lesions leading not necessarily to epileptogenesis but resulting in the impairment of learning and memory consolidation, abnormal behavioral reactions and psychotic disorders [Timmons et al., Ir Med J, 2002]. If neuronal networks implicated, for instance, in epileptogenesis and learning process overlap, both processes may interfere [Majkowski, Epileptologia, 1995].

Epileptic focus and focal discharges may change the level of receptors and neuronal pathways. Changes in the level of $5HT_3$ receptors leading to alterations in the release of other neuromediators (CCK, GABA, dopamine, Ach) seem to play a key role. In particular, abnormalities of GABA release may enhance development of psychiatric disorders following epilepsy, and an altered level of dopamine receptors plays an important role in depression, schizophrenia and drug refractory epilepsy [Jaber et al., Neuropharmacology, 1996].

The mezolimbic pathway plays an important role in the regulation of emotional and cognitive behavior. Mezocortical pathway is associated with functions of learning and motivational behavior in animals. The changes in signal transmission *via* the above pathways following focal seizures may be one of the reasons of emotional and behavioral abnormalities [Tebartz Van Elst et al., Brain, 2002].

From clinical point of view, a type and number of epileptic seizures, the location of the epileptic focus as well as spreading of seizure and forced normalization are very important [Landolt, Dtsch Med Wochenschr, 1962; Krishnamoorthy et al., Epilepsia, 1999]. Psychotropic effect of antiepileptic drugs may be attributed to a dose-dependent non-specific activity, overdosing, specific activity in predisposed subjects or to abstinence syndrome. Probable predisposing factors are polytherapy, high dose and rapid dose increase, organic CNS damage, positive history to psychiatric disorders both in patients and their families [Bilikiewicz, Psychiatr Pol, 1997; Briellmann et al., Neurology, 2000; Marchetti et al., Epilepsy Behav, 2003; Adachi et al., Epilepsia, 2002].

Disturbances in the functioning of the endocrine glands in epilepsy

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Clinical course of epilepsy reveals its significant connection with the functions of the endocrine system. Hormones produced by the body may alter convulsive irritability of the brain and thus modify the clinical picture of the disease. An increase or decrease in the number of epileptic attacks may, to some extent, correspond to variations in hormone levels, especially in such periods of humans' life like puberty, phase of menstrual cycle, pregnancy or menopause. On the other hand, it has also been demonstrated that epileptic attacks themselves and interparoxysmal epileptic discharges influence the production and secretion of hormones, both in interparoxysmal period and directly after epileptic attack. It refers mainly to hormones of the hypothalamic-pituitary-adrenal axis [Daniels et al., in: Harrison's Principles of Internal

Medicine, 13th ed. New York: McGraw-Hill, 1994]. Interictal serum prolactin levels are normal in most patients with epilepsy. Interictal hyperprolactinemia has been documented in certain subgroups, such as hyposexual men with limbic epilepsy. Most generalized tonic-clonic seizures and complex partial seizures are associated with transient hyperprolactinemia, but simple partial seizures are less likely to do so. Also, complex partial seizures of frontal lobe origin, usually do not affect serum prolactin. Absence (including absence status), myoclonic, and akinetic seizures do not stimulate prolactin release. Serum prolactin is not elevated after nonepileptic seizures [Spark et al., Lancet, 1984; Leiderman et al., Epilepsia, 1990]. Cortisol levels rise after simulated seizures, generalized tonic-clonic seizures, febrile convulsions, and fever alone in children. Non-epileptic seizures do increase serum cortisol level. Measurement of plasma cortisol is diagnostically advantageous since cortisol remains significantly elevated for more than an hour postictally, whereas prolactin elevations are relatively brief [Pritchard et al., Ann Neurol, 1983; Culebras et al., Epilepsia, 1987; Rao et al., Neuroendocrinology, 1989]. Elevations of serum growth hormone occur after some generalized tonic-clonic seizures and complex partial seizures, but few studies have evaluated growth hormone systematically [Dana-Haeri et al., J Neurol Neurosurg Psychiatry, 1983; Pritchard et al., Ann Neurol, 1983]. Postictal elevation of luteinizing hormone was found in women and men, but follicle-stimulating hormone levels rose only in women [Dana-Haeri et al., J Neurol Neurosurg Psychiatry, 1983].

Hormone secretion is dependent on the type of epileptic attacks as well as on localization of primary lesion. Epileptic attacks, by inducing abnormalities in the functioning of the limbic system structures, disturb normal activity of the hypothalamic-pituitary-gonadal axis and cause such problems as fertility disorders and sexual dysfunctions. More than 50% of women who have temporal lobe epilepsy (TLE), have some forms of menstrual dysfunction, including amenorrhea, oligomenorrhea, abnormally prolonged or shortened cycle intervals, amd menometrorrhagia [Herzog et al., Neurology, 1986]. More than one third (35.3%) of cycles in women with TLE are anovulatory, as compared to 8.3% in controls. Anovulatory cycles are more common in TLE than in primary generalized epilepsy [Cummings et al., Epilepsia, 1995]. Fertility is reduced to 69–85% among women with epilepsy, primarily with TLE [Dansky et al., Epilepsia, 1980; Webber et al., Epilepsia, 1986]. Reduced potency and hyposexuality occur in 38–71% of men with epilepsy [Fenwick et al., Acta Neurol Scand, 1985]. Because of their influence on enzymatic systems of the liver, antiepileptic drugs applied in the treatment are capable of accelerating or slowing down metabolism of certain hormones. It refers to endogenous hormones as well as those introduced to the body in the form of contraceptives. This may result in libido reduction, disturbances in menstrual cycle, fertility disorders. On the other hand, such circumstances are responsible for failed hormonal contraception in epileptic women. Oral contraceptive failure rate is notably greater in women with epilepsy who take antiepileptic drugs than in untreated epileptic women and women in general population. Enzyme-inducing antiepileptic drugs induce microsomal enzymes that increase the catabolism of sex steroids by the liver and conjugation of sex steroids in the gut. Antiepileptic drugs also increase synthesis of sex hormone-binding globulin by the liver, thereby decreasing the biologically active portion of the steroid. Higher-dose, rather than minipill formulation birth control pills are recommended for women with epilepsy who take antiepileptic drugs [Coulam et al., Epilepsia, 1979; Mattson et al., JAMA, 1986]. Most women with epilepsy can become pregnant and have healthy children. However, their pregnancies are subject to more complications, they are more likely to have difficulties during labor, and there is a higher risk of adverse pregnancy outcomes. During pregnancy, one quarter to one third of women with epilepsy have an increase in seizure frequency [Schmidt et al., J Neurol Neurosurg Psychiatry, 1983]. Generalized tonic-clonic seizures place both mother and fetus at risk of hypoxia and acidosis. Women with epilepsy are at greater risk for obstetrical complications during pregnancy. Vaginal bleeding, hyperemesis gravidarum and preeclampsia occur more frequently in these patients [Bjerkdal et al., Acta Obstet Gynecol Scand, 1973]. The infants of epileptic mothers are at greater risk of a variety of adverse pregnancy outcomes. These include fetal death, congenital malformations, congenital anomalies, and developmental delay [Kalter et al., N Engl J Med, 1983; Kelly, Am J Med Genet, 1984].

Non-convulsive status epilepticus

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Non-convulsive status epilepticus (NSE) is a subject that provokes strong reactions, perhaps largely due to the relative lack of evidence and the surfeit of opinions.

Non-convulsive status epilepticus is a term that has been rightly discarded in the new diagnostic scheme, because it encompasses heterogeneous conditions which may be either focal or generalized [Engel, Epilepsia, 2001]. NSE is not synonymous with absence status epilepticus (ASE).

Typical ASE occurs only in patients with idiopathic generalized epilepsy (IGE) (the subcategories with typical absence seizures) and also in the syndrome of *de novo* ASE of late onset. This form of non-convulsive SE should be distinguished from atypical ASE, which occurs in the secondarily generalized epileptic encephalopathies, and from complex partial SE which occurs in focal epilepsy. The clinical symptoms of these three types overlap but the prognosis and response to treatment are different. The mechanisms underlying ASE are uncertain and may include both genetic and environmental factors. The termination of absence seizures has been hypothesized to be due to persistent activation of a depolarizing current in thalamocortical neurons that inactivates T-type calcium channels. SE could thus result from dysfunction of this channel or mechanisms that hyperpolarize thalamocortical neurons, like the decreased cortical inhibition, increased reticular thalamic neuronal activity or increased $GABA_B$ receptor activation on thalamocortical neurons [Shorvon et al., Epilepsia**,** 2005].

Absence status epilepticus occurs in 10–20% of cases of idiopathic generalized epilepsy and in as many as 50% of some IGE syndromes such as those manifesting phantom absences perioral myoclonia [Panayiotopulos, Medlink Neurology, 2004]. Both perioral myoclonia with absences and phantom absences are clinically significant because they are probably lifelong and are associated with a very high incidence (around 50%) of ASE that may escape diagnosis and appropriate treatment [Panayiotopulos, Epilepsia, 2005]. Nearly all patients are fully aware of this SE and know that it may inevitably lead to generalized tonic-clonic seizures (GTCS). The stage is unlikely to be considered as a genuine status epilepticus by the physicians in emergency departments. This confusional state lasting for hours and ending with GTCS creates significant diagnostic difficulties regarding its nature and cause. Causes to consider are intoxication, and psychogenic, metabolic or systemic disorder.

Typical (idiopathic) ASE in IGEs is defined as a prolonged (> 30 min), generalized non-convulsive seizure of impairment of the content of one's consciousness (absence) and generalized spike, polyspike-wave discharges in EEG. It should be emphasized that typical ASE is of many types with cognition impairment as a shared common symptoms. It can be subdivided to:

- typical absence status epilepticus with impairment of consciousness only
- myoclonic-atonic status epilepticus
- myoclonic-absence status epilepticus
- perioral myoclonic status epilepticus
- eylid myoclonic status epilepticus

Memory and higher cognitive intellectual functions, such as abstract thinking, computation and personal awareness, are the main areas of disturbances, which varies from very mild to very severe with intermediate states of severity occurring more often. Mild disturbances are experienced as a state of slow reaction, behavior and mental functioning.

The ictal EEG is characterized by usually regular and symmetrical 2 Hz GSWD, which is continuous or repetitive [Panayiotopulos, The Epilepsies, 2005].

Idiopathic ASE is commonly unrecognized or misdiagnosed. It is surprising how often physicians are deceived by general good appearance, alertness and cooperation of the patient. The duration of the episodes is quite variable but in the vast majority of patients it is not longer than 1 to 2 days. A clear history of generalized epilepsy in a patient or a history of confusion of variable duration before a generalized seizure is quite suggestive of ASE.

Absence status may occur in all ages but is probably more common in adults or elderly individuals. Much has been written about its *de novo* onset in the elderly. Importantly, it is often due to benzodiazepine

withdrawal. Patients with primary, generalized, idiopathic epilepsy who have been seizure-free for many years may eventually start to have seizures again and ASE is relatively common pattern in such patients.

"*De novo*" absence status of late onset is typically induced by toxic or metabolic precipitating factors in middle-aged or elderly subjects with no previous history of epilepsy. Patients often have a history of psychiatric illness with multiple psychotropic drug intake. The electroclinical characteristics and the immediate prognosis are variable. These episodes of ASE generally represent acute symptomatic seizures and may not recur if the triggering factors can be controlled or corrected. Long-term antiepileptic drug treatment may thus not be needed. Absence status with focal characteristics occurs in subjects with a pre-existing or newly developing partial epilepsy, most often of extra-temporal origin. The EEG shows bilateral but often asymmetric ictal discharges. The immediate prognosis is variable. Some of these cases are difficult to distinguish from complex partial status epilepticus of frontal lobe origin [Thomas, Rev Neurol, 1999].

Complex partial status epilepticus is rarer than generalized ASE. Patients have frequently recurring focal seizures with incomplete recovery between attacks, or a continuous "epileptic twilight state" with cycling between unresponsiveness and partial responsiveness. The ictal EEG reveals recurrent epileptiform patterns consistent with those encountered in isolated focal seizures. The commonest reasons for misdiagnosis between the two conditions are listed in Table 1.

The major distinguishing feature of atypical ASE is that it occurs mainly in children with symptomatic or cryptogenic generalized epilepsies, who also have a spectrum of other types of seizures. Most of the patients also have moderate or severe learning and physical handicaps. Interictal EEG is often very abnormal with slow background activity. Atypical SE is clinically characterized by fluctuating impairment of consciousness often with other ictal symptoms. The ictal EEG pattern is of slow (< 2.5 Hz) GSWD (generalized spike and waves discharges).

From clinical point of view, it is important to question all patients with generalized epilepsy, whose seizures are not fully controlled, and their families about the possible occurrence of confusional episodes, particularly preceding major attacks.

Numerous definitions have tried to delineate complex partial status epilepticus (CPSE). It is a prolonged epileptic episode in which fluctuating or frequently recurring focal electrographic epileptic discharges, arising in temporal or extratemporal regions, result in a confusional state with variable clinical symptoms. Delgado-Escueta and Treiman proposed cyclic type of CPSE and a non-cyclic continuous form. The cyclic type begins by clear-cut complex partial seizures, followed by a continuous twilight state with purposeful, reactive automatisms, frequently interrupted by staring, unresponsiveness, oro-alimentary and complex gestural automatisms. This type is in probable relation to a primary or secondary ictal disorganization of the amygdalo-hippocampal complex. The non-cyclic type is characterized by a prolonged confusional state without clear-cut fluctuation of the symptomatology, and may be of extra-temporal origin [Thomas, Neurology, 1999].

Simple partial status epilepticus (SPSE) is defined by partial seizures without impairment of consciousness or secondary generalization and with preserved neurovegetative regulation. Clinical expression depends on the localization of epileptic focus. Serial focal seizures are considered to merge into status epilepticus when two or more sequential seizures occur with persistence of interictal neurological symptoms or, if there is continuous seizure activity, after a 10 to 30 min period of time.

Non-convulsive forms are often a diagnostic challenge, because of their rarity and the need for extensive documentation. This group includes epileptic aphasia and SPSE with somatosensory, visual, auditory and affective symptomatology.

Epilepsia Partialis Continua or type 1 Kozhevnikov Syndrome is characterized by simple partial somatomotor seizures followed, in the same body parts, by focal segmental rhythmic intractable myoclonic jerks of cortico/subcortical origin. EPC may also constitute the expression of an acute metabolic disorder especially during nonketotic hyperglycemia. Some case reports have documented rare forms of simple partial non-convulsive status with various features, ictal fear being the most frequent symptom.

Complex partial status epilepticus (CPSE) is a very heterogeneous condition with variable symptomatology. Confusion of varying intensity can be associated with language disturbances and psychotic features such as visual or auditory hallucinations, delusions and even catatonia. Unpleasant affective symptoms, including anxiety, depression and even paranoid ideas with aggressiveness may be confined to temporal localization.

Focal (non-convulsive) status epilepticus of frontal lobe origin is of undetermined prevalence. It is mani-

fested by prolonged impairment of consciousness and inappropriate behaviors. Symptoms fluctuate in intensity and severity over time. Thomas [Rev Neurol, 1999] described two types of frontal lobe status epilepticus. The first and more common type is characterized by mood disturbances with affective disinhibition or affective indifference, which are associated with subtle impairment of cognitive functions without overt confusion. The EEG shows a unilateral frontal ictal pattern and normal background activity. In the second type, the impaired consciousness is associated with bilateral, asymmetric frontal EEG discharges on an abnormal background. The response to intravenous benzodiazepines is poor, while intravenous phenytoin successfully controls seizures in most patients.

The new ILAE diagnostic scheme recognizes four forms of focal status epilepticus:

– Epilepsia partialis continua of Kozhevnikov
– Aura continua
– Limbic status epilepticus
– Hemiconvulsive status with hemi-paresis

In all classifications, even after the first description as Panayiotopoulos syndrome, childhood autonomic status epilepticus is ignored.

Panayiotopoulos syndrome is childhood idiopathic benign susceptibility to focal, mainly autonomic, seizures and autonomic status epilepticus. Seizures comprise an unusual constellation of autonomic, mainly emetic, symptoms, behavioral changes, unilateral deviation of the eyes and other ictal manifestations. Consciousness and speech as a rule are preserved at seizure onset. The seizure commonly starts with autonomic manifestations, which are mainly emetic. Child usually looks pale and vomits. Nearly half of seizures last for more than 30 min and can persist for up to 7 h constituting autonomic status epilepticus [Panayiotopulos, Pediatr Drugs, 2001].

Non-convulsive SE is underdiagnosed. An electroencephalogram should be obtained immediately in anyone with unexplained alteration of behavior or mental status and after convulsive SE if the patient does not rapidly awaken. Delay in diagnosis of SE is associated with a worse outcome and a higher likelihood of poor response to treatment. For refractory SE, continuous intravenous midazolam and propofol (alone or in combination) are rapidly effective. Randomized trials are needed to determine the best treatment for SE after lorazepam.

Drugs that enhance GABAergic transmission are recognized to promote absence seizures in patients with generalized epilepsy syndromes and may on occasions even induce NCSE. However, the ability of tiagabine (TGB) to also induce NCSE in focal lesional epilepsy is not widely recognized in clinical practice. To determine whether antiepileptic treatment with tiagabine is associated with an increased frequency of nonconvulsive status epilepticus in patients with refractory epilepsy, Koepp et al. [Epilepsia, 2005] reviewed retrospectively the medical and electroencephalographic (EEG) records of all inpatients with refractory localization-related epilepsy at the National Society for Epilepsy treated with TGB between January 1997 and December 2000. Clinical and EEG data before, during, and after TGB therapy were evaluated in those patients who experienced a deterioration in seizure control suggestive of NCSE. Frequency of NCSE was determined in a comparable, non-TGB-treated patient population. Seven (7.8%) of 90 TGB-treated patients were identified who experienced episodes of electroclinically confirmed NCSE. Serial EEGs showed deterioration during TGB treatment, with resolution of abnormality on discontinuation of TGB in all seven patients. During the same observation period, 32 (2.7%) of 1,165 non-TGB-treated patients developed electroclinically defined NCSE.

Although NCSE has been described in the literature for many years, there is still a great need for carefully designed prospective studies to help define clear guidelines to assist in clinical and therapeutic decisions making and, ultimately, to improve outcomes.

New strategy of diagnostic and therapeutic procedures in psychiatric disorders in epilepsy

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The questions concerning the relationships between the psychiatric disorders and epilepsy have been the subject of many studies of interdisciplinary teams. An interest in associations between epilepsy and psychiatric disorders can be tracked back to ancient times. The history of changing ideas on these relations between epilepsy and the psychiatric functions was divided into five periods [Majkowski, Padaczka, PZWL 1986 – in Polish]. These ideas are reflected by up-to-date investigative trends but nowadays there is an opportunity to verify these associations in both, experimental and clinical studies. These diseases may be linked in many ways [Majkowski, Epileptologia, 1993]. The pathomechanism of these relations is extremely complex and etiology of these disorders includes a wide spectrum of biological, psychological, social, and medical determinants. Also, the factor of epileptic activity, which may produce a variety of neurobehavioral changes and disturbed psychological well-being, is of considerable importance [Kaczyńska-Haładyj, Doctoral thesis, Medical University of Lublin, 1988].

The prevalence rates of psychiatric disorders in epilepsy reported by various researchers have fluctuated in the wide range from 6 to 74%. Numerous studies have indicated that the patients with epilepsy are at risk of several psychiatric disorders [Hermann et al., Epilepsia, 2000; Kanner et al., Epilepsy Behav, 2000; Marsh et al., Epilepsy Res, 2002; Giliam et al., Epilepsy Behav, 2003]. The psychopathology and corresponding symptomatology may evolve over time [Majkowski, Epileptologia, 1993]. The psychiatric symptoms characteristic of the neurobehavioral syndrome of epilepsy may also tend to be classified as atypical, episodic and pleomorphic events and of typical psychopathology of the psychiatric disorder. They may be brief or prolonged.

Several large studies have estimated that the rate of affective disorders is higher in patients with epilepsy than in those suffering from other chronic disorders [Trimble, Psychiatric Dev, 1987; Gaitatzis et al., Epilepsia, 2005]. Various mood disorders including depression and anxiety occur in up to 50–60% of patients with chronic epilepsy. The relationship between depression, anxiety and epilepsy is complex. It is necessary to distinguish the precital, ictal and postictal depression related to epilepsy from other psychiatric disturbances. Pre-ictal depression and irritability that occur hours or days before a seizure may be relieved by the convulsion. The pre-ictal dysphoria can last for several days. Ictal depression can occur rarely as a part of an aura, and is more common in patients with temporal lobe epilepsy. Post-ictal depression can last from hours to days and has features of a depressive phenomenology. The psychopathology of depression can be deep and some patients may express suicidal thoughts and attempts. There are groups of patients in whom post-ictal depression continues into prolonged affective disorders. The importance of understanding depression in epilepsy is highlighted by the fact that the suicide rate in patients with epilepsy is greater than in general population [Pompili et al., Epilepsy Behav, 2005]. The risk of suicide proved higher for patients with temporal lobe epilepsy, mental retardation and in the early years of these conditions [Barraclough, Acta Psychiatr Scand, 1987].

Anxiety disorders are more common then depressive disorders in patients with epilepsy. Despite the high prevalence of anxiety disorders in epileptic patients, there are no systematic studies or evidence-based guidelines for the treatment practice. The up-to-date study, assessing the psychopathology using a standardized diagnostic interview in patients with all types of epilepsy, estimated prevalence of anxiety at about 25% and that of mood disorders at 19% [Swinkels et al., Epilepsy Behav 2001]. The etiological factors need to be considered individually in each case with special focus on the preexisting vulnerability, predisposition, neurobiological factors, iatrogenic influences and psychosocial events. It is now recognized that anxiety can have a significant influence on the quality of life of patients with epilepsy [Choi-Kwon et al., Acta Neurol Scand, 2003; Johnson et al., Epilepsia, 2004].

The association between epilepsy and psychosis has been studied since the nineteenth century. The categorization into ictal, postictal and interictal psychosis is clinically very important, useful and allows for the tailored and comprehensive management. The majority of investigators support a relationship with temporal lobe epilepsy and some suggest risk factors such as severe and intractable epilepsy, epilepsy of early onset, secondary generalization of seizures, used anticonvulsant drugs, and temporal lobectomy [Slater et al., Br J Psychiatry, 1963; Bruens, Psychiatry Neurol Neurochir, 1971; Shukla et al., Br J Psychiatry, 1979; Toone, Br J Psychiatry, 1982; Roberts et al., Biol Psychiatry, 1990]. Newer neurophysiological and neuroimaging techniques have not yet been sufficiently applied to the psychoses in epilepsy.

The large population study has shown that people with epilepsy have a higher prevalence of schizophrenia-like psychosis compared with general population [Jalava et al., Epilepsia, 1996; Bredkjaer et al., Br J Psychiatry, 1998; Sachdev, Am J Psychiatry, 1998]. Currently, examinations of this relationships are in progress and the proposed pathogenetic mechanisms are under evaluation.

The relative risk of schizophrenia or schizophrenia-like psychosis tended to be higher in people with multiple admissions for epilepsy, and particularly with increasing age at the first admission for epilepsy. There is a strong association between epilepsy and schizophrenia or schizophrenia-like psychosis. The two conditions may share common genetic and environmental causes [Qin et al., Br Med J, 2005]. The new five-axis classification scheme for the evaluation of psychopathology and epilepsy was reported by Japanese epileptologists [Matsuura et al., Epilepsy Behav, 2000]. They analyzed the group of 398 patients with epilepsy who were refereed to out-patient clinics. 42% of the subjects showed psychiatric disorders. The statistical analysis revealed that there were three risk factors predisposing for psychiatric disorders – mental disorders, temporal lobe epilepsy and high seizure frequency. Appropriate diagnosis of psychiatric disorders is essential for tailored strategy of management and for prognosis.

In the treatment of epilepsy-related psychiatric disorders, priority should be given to optimizing seizure control, then improved global and psychosocial functioning. Antidepressant and antipsychotic drug treatment may manifest convulsant and anticonvulsant effects. Pros and cons of pharmacological treatment with old and new generation antipsychotic and antidepressant drugs are still a matter of discussions.

Conclusions

Psychiatric conditions occur frequently in epilepsy, and their manifestations are diverse. Evaluation and management requires up-to-date knowledge of disease process relevant to epilepsy and to psychiatry as well as of the role of pathological factors that affect the expression of psychiatric illnesses: behaviors, temperament, cognition, and life events. Understanding of the interrelationships between co-morbidities, epilepsy, and their treatments is essential to optimal management of patients with epilepsy.

Genetic aspects of epilepsy

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Genetic factors are thought to play an important role in the etiopathogenesis of idiopathic epilepsy. It has been well established that numerous genes whose mutations lead to disturbances in brain development, metabolism, neurodegenerative processes and defective neuronal activity are frequently associated with certain inherited forms of epilepsies. Special attention has been paid to channelopathies that are due to the mutation of subunits of neuronal voltage-dependent sodium, potassium, calcium and chloride channels. A single amino acid mutation may significantly change ion channel conductance, its kinetic parameters and

the affinity of agonists and antagonists. For example, it has been reported that the substitution of lysine with methionine in the gamma2 subunit of the $GABA_A$ receptor decreases IPSP, whereas the substitution of alanine with asparagine in the alpha1 subunit decreases $GABA_A$ receptor sensitivity, prolongs the time of desensitization and shortens the opening time for chloride channels. Defects in the same locus seem to be reflected in the heterogeneous phenotype; on the other hand, the same epileptic syndrome may be caused by various genetic defects. Benign familial neonatal or infantile convulsions (BFNC or BFIC), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), absence epilepsy, myoclonic epilepsies, generalized idiopathic epilepsies and febrile seizures are the best-known, genetically determined epilepsy syndromes [Jóźwiak et al., Neur Neurol Pol, 2005]. Moreover, epilepsy is one of the main symptoms of many other genetic diseases, e.g., cereidolipofuscinosis, galactosialosidosis or gangliosidosis GM1.

Further identification of gene mutations associated with spontaneous seizures may be helpful not only in classifying more precisely idiopathic epilepsies, but also in evaluating prospective animal models of these neurological diseases.

Possible interaction between chronic treatment with vigabatrin and conventional antiepileptic drugs

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Vigabatrin is a novel antiepileptic drug, which increases GABA level by an irreversible inhibition of GABA-aminotransferase. The aim of this study was to evaluate the effects of acute or chronic treatment with vigabatrin on the anticonvulsant activity of valproate, ethosuximide and clonazepam against pentetrazole (PTZ)-induced seizures in mice. In addition, we investigated the effects of antiepileptic drugs alone or in combinations with vigabatrin on motor performance. Chemical seizures were induced by a subcutaneous injection of pentetrazole at its CD_{97} and defined as a clonus of the whole body with an accompanying loss of righting reflex, lasting for over 3 s. It was previously described that acutely given vigabatrin inhibited the clonic phase of pentetrazole-induced seizures and ED_{50} of the drug was 879 mg/kg. Moreover, vigabatrin (at the subthreshold dose of 250 mg/kg) potentiated the protective activity of ethosuximide, reducing its ED_{50} value from 142 to 95 mg/kg against clonic phase of PTZ-induced seizures, but simultaneously elevated its plasma level [Świąder et al., Pol J Pharmacol, 2003]. The protective activity of valproate and clonazepam remained almost unchanged [Świąder et al., Pol J Pharmacol, 2003]. Similarly, 7-day treatment with vigabatrin (at the subthreshold dose of 75 mg/kg or 125 mg/kg) did not affect the anticonvulsant activity of conventional antiepileptics. Vigabatrin, given acutely or chronically, significantly decreased TD_{50} (toxic dose which is the dose causing the impairment of motor coordination in 50% of the animals tested) of ethosuximide and clonazepam in the chimney test, having no impact on this parameter in combination with valproate. Potentiation of the ethosuximide's protective activity was presumably due to a pharmacokinetic interaction.