CONFERENCE REPORT

Fourth Conference on Epileptogenesis, May 23–26, 2007, Pisa, Italy

The Fourth Conference on Epileptogenesis was aimed at discussing new and controversial issues in the area of epileptogenesis research in the format of a workshop. Epileptogenesis is a particularly integrative field of research, in which experimental data and clinical evidence are brought together to provide insight into pathological plasticity phenomena and, more broadly, into the mechanisms of brain adaptation to environmental stimuli.

The conference was opened by Lamberto Maffei, who presented an overview on the mechanisms regulating the postnatal development and plasticity of the rodent visual system. Visual system development and plasticity have been shown to depend largely on a proper sensory experience during early postnatal life. Recent studies have demonstrated the positive effects of environmental enrichment on the maturation and function of the visual system (Sale et al., 2007). These studies have profound implications for understanding both physiological and pathological development of CNS.

The first session addressed the role of ion channels and transporters in epileptogenesis. Aristea Galanopoulou presented a study on the effects of the expression of KCC2 on GABA function in brain development. During development, $GABA_A$ receptors mediate depolarizing neuronal responses, whereas in the adult they are hyperpolarizing. The switch from depolarizing to hyperpolarizing $GABA_A$ receptor signaling is triggered through the developmental shift in the balance of intracellular chloride cotransporters. The maturation of $GABA_A$ signaling follows sex-specific patterns correlated with expression profiles of chloride cotransporter KCC2 (Galanopoulou, 2007), suggesting that $GABA_A$ receptor activation may be differentially regulated in males and females. This finding has particular implications in epilepsy, since $GABA_A$ receptor activation by antiepileptic drugs may differentially influence brain development in males and females. The role of calcium channels in epileptogenesis was discussed by Heinz Beck. In the pilocarpine model of temporal lobe epilepsy (TLE), a conversion from regular to burst firing (that is likely to play a role in TLE ictogenesis) was observed in hippocampal CA1 pyramidal neurons. Specific changes in the expression and properties of Cav3.2 T-type Ca2+ channel subunits were also detected (Su et al., 2002). Patch-clamp analyses of CA1 neurons from pilocarpine-treated mice revealed that the burst-firing mode does not occur in mice lacking Cav3.2 channels. Moreover, the frequency and severity of chronic seizures, as well as the neuropathological sequelae were significantly attenuated in chronic epileptic Cav3.2 knockout mice, suggesting that Cav3.2 up-regulation after SE may contribute to initiation of seizure activity and neuronal cell death in chronic epilepsy. Potassium channel subunits mediate neuron repolarization following action potential discharge, and their mutations give rise to different types of seizure disorders in humans and in mouse models. The mechanisms underlying potassium channelopathies, discussed by Jeff Noebels, involve modified patterns of sustained repetitive firing properties in both excitatory cells and interneurons. Examples of mouse models include targeted deletion of the *Kcna1, Kcnc2, Kcnq2/3*, and the *Kcnmb4* genes (mediating Kv1.1, Kv 3.2, Kv7.2/3, and BK currents, respectively). Since human epilepsy is often the product of complex or multigenic inheritance, it is crucial to analyze how mutations in more than one channel may interact. One new example of a digenic mouse model, involving Kcn1a and Cacna1a genes reveals multiple levels of physiological interaction leading to partial masking of the seizure phenotypes in these mutants (Glasscock et al., 2007). HCN1/HCN2 channel subunits responsible for hyperpolarization-activated current (I_h) are expressed at high density in dendrites and regulate overall dendritic excitability. As discussed by Daniel Johnston, I_h is partly active at resting potential and acts globally on dendritic inputs. These properties of I_h determine its ability to influence synaptic potentials in both hyperpolarizing and depolarizing membrane potential ranges. Temporal summation of excitatory synaptic potentials is reduced by I_h, regardless of the dendritic location of synapses. Long-term changes in the expression of I_h in pyramidal neurons of CA1 and entorhinal cortex have been demonstrated in acute and chronic models of TLE. I_h decreases and redistributes from dendrites to soma, significantly altering the oscillatory properties of pyramidal neurons, both in conditions of normal excitability (during long-term potentiation) and during epileptogenesis (Shah et al., 2004). Mutations in nicotinic receptor channels have also been associated with the epileptic phenotype. In particular, a missense mutation in the $\beta 2$ subunit of neuronal nicotinic receptor (*CHRNB2*) was demonstrated in patients affected by autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), a focal form of

epilepsy characterized by seizures occurring during sleep and originating from the frontal lobe (De Fusco et al., 2000). Irene Manfredi presented a new transgenic ADNFLE mouse model generated by using the TET-OFF system. EEG recordings from transgenic mice expressing the mutant $\beta 2$ subunit reveal frequent spikes and spontaneous seizures. Preliminary evidence shows the possibility to revert the epileptic phenotype by chronic oral administration of doxycycline, a compound known to silence the transgene. Neurons with long-range connections are essential for transiently "binding" different brain regions and could also play a key role in pathological synchronizations, such as epileptic seizures. Christophe Bernard reported that transient fast oscillations at seizure onset in the immature hippocampus result from the high-frequency firing of most of the GABAergic interneuron population (Cossart et al., 2005). A specific class of long-range interneurons (hippocampus-septum cells), whose axon arborizes in the whole hippocampus and in the septum, is necessary to entrain other interneurons into high frequency firing. Destruction of these cells abolishes fast oscillations but not seizures, providing evidence that neurons with long-range connections control synchronized oscillations. These studies suggest that fast oscillations are not necessary for ictogenesis, but rather constitute a signature of network activity.

The second session addressed different aspects of brain development implicated in epileptogenesis, Renzo Guerrini presented data on genetic disorders of cortical development associated with epilepsy. X-linked periventricular nodular heterotopia (PNH) consists of confluent nodules of gray matter located along the lateral ventricles and is often associated with focal epilepsy. Filamin (*FLN1*) mutations have been reported in both familial and sporadic cases. A recessive form of PNH due to *ARGEF2* gene mutations has also been reported in children with microcephaly, severe delay and early-onset seizures. Lissencephaly-pachygyria and subcortical band heterotopia (SBH) result from mutations of either the *LIS1* or *XLIS* gene. Finally, X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia is associated with mutations of the *ARX* gene (Barkovich et al., 2005; Guerrini & Marini, 2006). Antonio Simeone discussed the role of homeobox-containing transcription factors of the *Otx* family in glutamatergic versus GABAergic differentiation during development. Genetic ablation of *Otx2* in glutamatergic progenitors of the thalamus results in the expression of GABAergic markers in these cells. Reported data suggest that *Otx2* may prevent GABAergic fate switch by repressing the *Mash1* gene in glutamatergic progenitors (Puelles et al., 2006). Genetic mechanisms regulating the generation of GABAergic neurons were also addressed by Inma Cobos, who focused on the role of *Dlx* homeobox transcription factors. Cortical interneurons express *Dlx1* and *Dlx2* during development and into adulthood, and their differentiation depends on the number of expressed copies of these genes. *Dlx1-/-;Dlx2-/-* double mutant mice show defects in the differentiation and survival of GABAergic interneurons, and a migration arrest of immature interneurons from the subpallium to neocortex and hippocampus. Conversely, interneurons in *Dlx1-/-* mutants show no migration defects, but subsets of them fail to survive. *Dlx1-/-* mice exhibit generalized seizures and seizure-induced reorganization, linking the *Dlx1* mutation to delayed-onset epilepsy associated with interneuron loss (Cobos et al., 2005, 2007). Rafael Gutierrez discussed the significance of the glutamate/GABA switch in epilepsy. As a consequence of seizures, glutamatergic granule cells of the dentate gyrus (DG) produce GABA and GABAergic markers (GAD67, vGAT), and elicit $GABA_A$-receptor-mediated responses in CA3. During the first postnatal weeks, GABAergic input to dendrites of CA3 pyramidal cells in the stratum lucidum (SL) evokes depolarizing postsynaptic potentials, due to the persistent expression of the NKCC1 cotransporter in CA3 dendrites. Conversely, in adult rats, the DG tonically inhibits CA3 activity through GABA-mediated signaling. Thus, the release of GABA from mossy fibers may contribute to increased seizure susceptibility in the early postnatal period (Gutierrez, 2005; Trevino et al., 2007). Giulia Curia described altered GABAergic function in *fmr1* knockout (KO) mice, a model of fragile X syndrome. In the subiculum, $GABA_A$ receptor-mediated phasic and tonic components are different in *fmr1* KO as compared to wild-type mice. In addition, the expression of subunits involved in GABAergic tonic inhibition is down-regulated in the subiculum of *fmr1* KO mice. Thus, alterations in GABAergic transmission occurs in fragile X animals, suggesting that different expression of $GABA_A$ currents may lead to hyperexcitability and epilepsy in fragile X patients. Tamar Chachua presented data on the effect of thalamic stimulation on the generation of seizure activity. Some GABAergic neurons of the thalamic reticular nucleus (TRN) fire at high frequency during the silent periods of clonic discharge and at the end of generalized seizures induced by hippocampal kindling. TRN stimulation during hippocampal kindling induces marked suppression of limbic motor seizures due to potentiated activity of TRN inhibitory neurons (Nanobashvili et al., 2003). The last two presentations in this session addressed the role of synaptic vesicle proteins in epilepsy. Mutations in the synapsin 1 and 2 genes have been identified in families of patients with partial temporal lobe or frontal lobe epilepsy (Garcia et al., 2004), and deletion of synapsin genes is associated with epilepsy in mice (Rosahl et al., 1995). Fabio Benfenati showed that patch-clamp recordings on cultured hippocampal neurons from synapsin KO mice reveal a reduced amplitude of evoked inhibitory postsynaptic currents. These results are reflected by a marked increase in bursting activity of synapsin KO networks in culture, as compared to wild-type networks. These data indicate an involvement of synapsins

in the balance between inhibitory and excitatory transmission and suggest that they play a role in the etiology of human epilepsy. Flavia Antonucci discussed the neuroprotective effects of botulinum neurotoxin E (BoNT/E, a protease that blocks neurotransmitter release via cleavage of the synaptic protein SNAP-25) in a mouse model of TLE. Intrahippocampal delivery of BoNT/E after kainic acid-induced status epilepticus (SE) delays epileptogenesis without preventing the occurrence of chronic seizures. However, BoNT/E significantly reduces granule cell dispersion, CA1 cell loss and reelin down-regulation that occur after SE (Antonucci et al., 2008). These findings suggest that specific morphogenetic changes following SE are not implicated in epileptogenesis.

In the third session, innovative strategies to inhibit ictogenesis and possibly epileptogenesis were presented. Karen Gale discussed the effects of electroconvulsive shock (ECS) preconditioning on the long-term outcomes of SE. Chronic, but not acute, exposure to minimal ECS prevents neuronal damage induced by subsequent SE, presumably via transcriptional up-regulation of fibroblast growth factor-2 (Kondratyev et al., 2002). Evidence on the role of chromatin modifications (such as phosphorylation of histone variant H2A.X; Crowe et al., 2006) in epileptogenesis after ECS-preconditioning and SE was also presented. Michael Rogawski described the potential use of convection-enhanced delivery (CED) for the treatment of focal epilepsy. CED consists in delivering therapeutic substances to a localized brain region by slowly infusing a solution under positive pressure through a fine cannula. N-type calcium channel toxins and botulinum toxins were delivered using CED in fully kindled animals, resulting in a dose-dependent increase in the afterdischarge threshold and a decrease in its duration. Behavioral seizure score and duration were also decreased up to 1 week for calcium channel toxins and up to 50 days for botulinum toxins (Gasior et al., 2007). Jana Veliskova described the anticonvulsant and neuroprotective effects of β-estradiol. Administration of β-estradiol to ovariectomized females in doses producing physiological concentrations, delays seizure onset and prevents SE-induced damage of hippocampal neurons. Neuroprotection includes the damage-sensitive subpopulation of neuropeptide Y (NPY)-containing hilar interneurons. Parallel effects of β-estradiol and NPY suggest a possible estrogen-NPY interaction (Velísková & Velísek, 2007). Mireille Lerner-Natoli addressed the role of angiogenesis and blood-brain barrier (BBB) function in epileptogenesis. Neovascularization and loss of BBB integrity was found in hippocampi from TLE patients, as compared to hippocampi from nonepileptic subjects (Rigau et al., 2007). These alterations positively correlated with seizure frequency. Vascular endothelial factor (VEGF) and tyrosine kinase receptors were highly expressed by neurons and endothelial cells, respectively, and might be implicated in neovascularization. Accordingly, VEGF overexpression and BBB impairment occurred early after experimental seizures in rats, followed by a progressive increase in vascularization which was maintained in chronically epileptic tissue. Robert Schwarcz illustrated the functional changes in glial cells occurring in the brain of patients suffering from chronic epilepsy and in various animal models of the disease. These changes, which affect both microglial cells and astrocytes, have been traditionally viewed as being secondary to neuronal loss and of little if any functional significance. Recent studies, however, indicate that selective glial changes frequently precede seizure activity and seizure-induced neurodegeneration; activated glial cells produce and release neuroactive metabolites which can influence seizure threshold and neuronal viability, and abnormal glial cells can be targeted selectively for the focal delivery of antiepileptic principles (Schwarcz & Pellicciari, 2002). Barbara Gagliardi described the interleukin-1 system as a novel pathway involved in ictogenesis and possibly in epileptogenesis, which may offer a nonconventional antiepileptic approach (Vezzani & Baram, 2007). IL-1β is rapidly synthesized by glia in rodent brain during acute seizures, and its production persists during epileptogenesis and in chronic epileptic tissue. When injected into the rodent hippocampus, IL-1 has proconvulsant effects, while inhibition of its signal transduction pathway or blockade of its endogenous synthesis affords significant anticonvulsant and antiepileptogenic effects. Eleonora Palma, using membrane extracts from the brain of epileptic patients microtransplanted into Xenopus oocytes, provided electrophysiological evidence supporting the hypothesis that rundown of $GABA_A$ receptors is a pathologically relevant dysfunction for epilepsy (Palma et al., 2005).

The fourth session of the meeting focused on neuronal damage and repair in acquired epilepsies. Asla Pitkänen investigated whether changes in magnetic resonance imaging (MRI) could be used to predict posttraumatic epileptogenesis and cognitive decline in the traumatic brain injury (TBI) model. From all MRI parameters analyzed, changes in postinjury diffusion trace (D_{av}) in the hippocampus were most consistently associated with the long-term outcome (spike activity, mossy fiber sprouting, memory impairment) (Kharatishvili et al., 2007). Thus, damage severity measured with MRI may predict seizure susceptibility and cognitive outcome after TBI. Many preclinical studies on acquired epilepsies use convulsive SE as an epileptogenic stimulus. However, convulsive SE fails to reproduce many important features of the human disease. To develop better animal models, Robert Sloviter hypothesized that human-pattern hippocampal sclerosis (HS) is the result of less than maximally intense excitation—a level of excitation that activates the hippocampus but stays sequestered within temporal circuits (in contrast to convulsive SE, which evokes seizure activity predominantly in extrahippocampal pathways). Sloviter described two new

animal models that approximate the features of human TLE, both models involving perforant path stimulation and having the advantages of minimal variability, minimal lethality, spontaneous hippocampal-onset seizures, and human-pattern HS (Sloviter et al., 2007). If cell loss is a critical factor for the development of epilepsy, one may expect that neurogenesis represents an insufficient attempt to halt the process by repairing the damage. Jack Parent is studying the influence of neurogenesis in the epileptic adult hippocampus. Increased precursor cell proliferation and ectopic location of mature granule cells in the hilus and in the molecular layer was found in pilocarpine-treated adult rats (Parent et al., 2007). These ectopic cells look remarkably similar in epileptic human and rat DG. Anatomical studies indicated that ectopic adult-born neurons integrate long-term and persistently exhibit abnormal properties (Jessberger et al., 2007). Thus, neurogenesis in the epileptic hippocampus is not only insufficient, but also altered, and likely contributes to seizures. This conclusion leads to the idea that endogenous neurogenesis should be supplemented and/or guided toward a therapeutic aim (tissue repair). One approach for supplementation is the transplant of cells. Ashok Shetty used hippocampal fetal cell (HFC) grafting for repairing damage and treating chronic TLE. He quantified survival and antiseizure effects of HFC grafts transplanted into the hippocampi of rats displaying spontaneous recurrent seizures (SRS) following kainate-induced SE. HFCs treated and grafted with neurotrophic factors and a caspase inhibitor (but not standard HFC grafts) survived well, differentiated into neurons and blunted the progression of TLE (Rao et al., 2007). Thus, grafting of precursor cells into the hippocampus might be effective in restraining SRS in chronic TLE. The alternative approach—guiding the endogenous progenitors to survival and integration—has been explored by Beatrice Paradiso. Once epileptogenic damage was established, she injected in the hippocampus a herpes vector engineered to locally supplement two neurotrophic factors, FGF-2 and BDNF (a mitogenic and a neuro-differentiating agent for neural progenitors). This treatment increased neuronogenesis, repaired neuronal damage and prevented epileptogenesis (Paradiso et al., 2008). Another interesting vector type may be based on adeno-associated virus (AAV). Merab Kokaia reported advancements on one such vector supplementing NPY, a homeostatic agent for synaptic transmission and plasticity. When overexpressed in the rat hippocampus using recombinant AAV (rAAV) vectors, NPY exerts antiepileptic and antiepileptogenic effects. Interestingly, hippocampi overexpressing NPY have a partial reduction of LTP magnitude, due to activity-dependent release of transgene-mediated NPY, thus decreasing glutamate release. These studies suggest that a rAAV-based gene therapy approach using NPY could be useful for treating intractable forms of epilepsy. Finally, Marzena Stefaniuk presented preliminary data from a large microarray screening study aimed at identifying novel epileptogenesis-related genes in the rat brain. Samples were collected at 1, 4, or 14 day after kainic acid or pilocarpine-induced SE.

Recent experimental evidences demonstrated that glial cells exert a primary role in the control of neuronal excitability. An update of the new findings on glia and the control of epileptic activity was the topic of the last session of the conference. Giorgio Carmignoto focused on the interactions between glia, neurons, and brain vessels (Haydon & Carmignoto, 2006). Following neuronal activity, glutamate-mediated Ca^{2+} elevations in astrocyte processes are transferred to astrocyte endfeet that contact cerebral blood vessels and control their tone (Zonta et al., 2003). Interictal and ictal discharges exert different effects on astrocytes in entorhinal cortical slices. Ictal events triggered a highly synchronized Ca^{2+} response in astrocyte endfeet along the entire length of the blood vessel, followed by a rapid arteriole response. In contrast, interictal events triggered only discrete Ca^{2+} oscillations in endfeet, accompanied by rare and spatially restricted responses of the arteriole. Astrocytes thus may regulate cerebral blood flow in the epileptic brain. Glial cells can, by multiple functions, influence neuronal excitability. Uve Heinemann reported on spatial K^+ buffering, i.e., the facilitated redistribution of potassium from sites of maximal K^+ release to remote sites where extracellular potassium is low. Astrocytes expressing glutamate transporters (Glu-T type) are involved in spatial K^+ buffering, mostly through K_{ir} 4.1 and 2P channels. Spatial K^+ buffering is strongly reduced when K_{ir} channels are blocked, an effect which can be augmented by additional blockade of 2P channels. This effect is often missing in chronic epileptic tissue, likely as a result of altered BBB permeability. Following artificial BBB opening, astrocyte activation correlates with a strong down-regulation of K_{ir} channels and disturbed K^+ buffering. As a result, increased K^+ accumulation and appearance of epileptiform discharges can occur (Ivens et al., 2007). The relevance of altered functional astrocyte properties to seizure generation in postsurgical specimens of human hippocampi was addressed by Christian Steinhäuser. Astrocytes can be differentiated in two populations, one coupled via gap junctions and expressing glutamate transporters (GluT-type), and the other expressing AMPA-type glutamate receptors and receiving direct synaptic inputs from neurons (GluR-type). In human hippocampal specimens obtained from patients with pharmaco-resistant TLE, GluR- and GluT-like cells could be detected in nonsclerotic tissues. In contrast, in the hippocampus of patients with HS, GluT-type astrocytes disappeared, and GluR-cells displayed slower receptor desensitization (Seifert et al., 2004). Thus, in HS, the ability of astrocytes to clear the extracellular space of glutamate and K^+ is dramatically impaired, therefore facilitating the generation and spread of seizure activity (Seifert et al., 2006). Glial

cells express receptors for neurotransmitters that are activated through spillover or release from extrasynaptic sites. Dwight Bergles provided evidences that neurons in the hippocampus, cortex, and cerebellum form direct synaptic junctions with glial progenitor cells known as "NG2+ cells." These junctions may provide a means to couple neuronal activity to changes in the proliferation and behavior of these glial progenitors. Alternatively, abnormal activity may lead to changes in the local environment, which alter the fate of these cells. Chemically induced seizures cause the appearance of periodic bursts of EPSCs in NG2+ cells in the hippocampus, suggesting that abnormal neuronal activity may trigger changes in these progenitors, altering both their association with neuronal elements and their fate in the mature CNS (Paukert & Bergles, 2006; Ziskin et al., 2007). Giuseppe Biagini described the modulatory effects of neurosteroids on epileptogenesis. Neurosteroids are mainly contained in glial cells. In brains from animals experiencing SE, the limiting enzyme for neurosteroid production (cholesterol side-chain cleavage cytochrome P450, P450scc), is up-regulated in astrocytes in the hippocampus and extrahippocampal areas. P450scc immunostaining of oligodendrocytes and microglial cells increased progressively after the SE. Treatment of SE animals with finasteride (5α-reductase inhibitor of neurosteroid synthesis) determined an earlier occurrence of seizures in comparison to the vehicle-treated animals (Biagini et al., 2006). Finally, Laura Uva discussed the role of BBB impairment in pilocarpine-induced SE (Marchi et al., 2007). When pilocarpine was applied by arterial perfusion to the in vitro isolated guinea pig brain, no epileptiform activity was induced, unless drugs that increase BBB permeability, such as histamine and bradykinin were coperfused. The data discussed suggest that an increase of BBB permeability could play a crucial role in promoting seizure activity, possibly through an increase of pilocarpine concentration in brain parenchyma.

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LETTERS/COMMENTARY

Use of propofol anesthesia and adjunctive treatment with levetiracetam and gabapentin in managing status epilepticus in a patient of acute intermittent porphyria

CASE REPORT

A 12-year-old boy presented to us in the emergency with a 3-day history of progressive drowsiness and intermittent generalized seizures followed by status epilepticus of 1 day duration. He had been suffering from seizures since the age of 2 years. He had had two episodes of status epilepticus in the past year. His birth and developmental history was normal. He had a poor scholastic performance and was short-tempered by nature. He had suffered from recurrent severe abdominal pain for 2 years for which a laparotomy had been performed previously. He was diagnosed as having porphyria during an episode of status epilepticus 1 year previously based on a positive urinary test for porphobilinogen and had been receiving gabapentin and levetiracetam ever since. An MRI done 1 year previously had shown a small nonenhancing T2W hyperintensity in the right medial frontal area.

The seizures were generalized and he was in persistent altered sensorium between the episodes. On examination, he was stuporose and intermittently flexing both limbs to deep painful stimulus. His pupils were 4 mm bilaterally and reacting sluggishly. Doll's eye maneuver was present but sluggish. Fundus examination was normal. Tone was decreased in all four limbs and all deep tendon jerks were elicitable. Plantars were bilaterally extensor. He was initially given bolus lorazepam during a seizure in the emergency following which the seizure terminated but recurred again within a few minutes. He was immediately shifted to the ICU, intubated and put on a ventilator. Propofol bolus followed by infusion at a rate 1.5 mg/kg/hr was started.

A ryles's tube was inserted and gabapentin 1,600 mg and levetiracetam 1,500 mg/day were continued. The diagnosis of porphyria was confirmed by a positive urine porphobilinogen on three consecutive samples. High dose dextrose was given intravenously as hematin was not available. Seizures recurred after 1 h and the dose of propofol was stepped up to 2 mg/kg/hr. Seizures were completely controlled with an infusion rate of 3 mg/kg/h which was continued for next 24 h. Continous EEG monitoring could not be done because of nonavailablilty. Liver function tests and serum triglycerides were closely monitored during the propofol infusion. Propofol was slowly tapered over the next 24 h and the patient remained seizure-free thereafter. A repeat CT scan performed in the present admission was normal. He remained normotensive throughout his hospital stay. He gradually improved in sensorium over the ensuing week and was discharged in a satisfactory condition after ten days having been advised to continue gabapentin and levetiracetam, and cautioned on the use of specific medications.

The porphyrias are a group of uncommonly inherited metabolic disorders in which there is disturbance of haem synthesis. Classic acute porphyrias include three different disorders: acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria; attacks of which are clinically indistinguishable from each other. (Kauppinen, 2005). In about 20% of patients, seizures may be one of the manifestations of acute intermittent porphyria (AIP). (Bloomer & Bonkovsky, 1989; Arora & Mahajan, 2000).

Table 1. Use of antiepileptic drugs in porphyria

Study	Study type	Result
Gabapentin		
Krauss et al., 1995	Case report	Safe
Tatum & Zachariah, 1995	Case report	Safe
Hahn et al., 1997	Experiment on primary chicken Embryo liver cells	Vigabatrine and gabapentin safe
Arora & Mahajan, 2000	Case report	Safe
Pandey et al., 2003	Case report	Safe
Levetiracetam		
Zaatreh, 2005	Case report, IV Magnesium+ Leviteracetam	Safe
Bilo L et al., 2006	Case report in patient with PCT	Safe
Oxcarbazepine[a]		
Gaida Hommernick, 2001	Case report	**Safe controversial

[a]Although there are case reports and articles (Lacerda et al., 2006) which report the above drug to be safe the list of drugs unsafe in porphyria listed in http://www.porphyria-europe.com and http://www.uct.ac.za/depts/porphyria report oxcarbazepine to be unsafe.

Table 2. Propofol use in studies

Author, year	Type of study	Conclusion
Shaw, 1998	Case report	Safe
Pandey et al., 2003	Case report	Safe
Bohrer et al., 1995	Study in rat model	Bolus dose safe

The relationship of seizures to porphyria is complex. Most common are acute symptomatic generalized seizures occurring in the context of AIP in relapse (Winkler et al., 2005). Several drugs with insignificant hepatic metabolism have been tried in the treatment of seizures due to porphyria, with good results (Table 1). However, all these drugs are available as oral preparations only and the treatment of status epilepticus in these patients therefore warrants the use of a rapidly acting drug which can be given parenterally and is safe in porphyria. Propofol was selected to control convulsions because it has been found to be effective in human as well as animal studies (Table 2). Propofol has barbiturate- and benzodiazipine-like effects on the delta-aminobutyric acid and can suppress central nervous system metabolic activity. There are conflicting reports in literature about porphyrogenecity of Propofol. Several reports show that a single induction dose has no adverse clinical effect. Bohrer et al., 1995, tested the porphyrogenecity of propofol in a primed rat model

Table 3. List of drugs to be avoided in Porphyria

Common drugs	Antiepileptic drugs
1. Sulfonamides	1. Carbamazepine
2. Synthetic estrogens and progesterone	2. Valproic acid
3. Barbiturates	3. Phenytoin
4. Griseofulvin	4. Lamotrigine
5. Alcohol	5. Topiramate[a]
6. Ergot derivatives	6. Ethosuximide
7. Methyldopa	7. Primidone
8. Pyrazinamide, rifampicin, dapsone	8. Oxcarbazepine[b]
9. Thiopentone	
10. Erythromycin	
11. Chloramphenicol	
12. Cotrimoxazole	
13. Aminophylline	

[a]Use only with extreme caution and if no alternative. There is only one study published so far done in rats that found topiramate less porhyrogenic than phenobarbitone, but increased hepatic pentoxyresorufin–O–dealkylase activity. Hence, administration of these drugs to patients with suspected porphyria should be avoided.

[b]Although there are case reports and articles (Lacerda et al., 2006) which report the above drug to be safe the list of drugs unsafe in porphyria listed in http://www.porphyria-europe.com and http://www.uct.ac.za/depts/porphyria report oxcarbazepine to be unsafe.

and concluded that it is safe in a porphyric patient when given as a single bolus dose. However, caution was advised with the use of large cumulative doses although, in 1992 Harrison & McAuley, 1992, reported sedation of a patient of AIP with propofol for 32 days without any major adverse events. The present case highlights the possible safety of this drug in managing a time-sensitive and serious condition like status epilepticus in a patient with suspected or proven porphyria. Adjunctive therapy with oral drugs, like levetiracetam and gabapentin should also begin as early as possible for maintenance therapy later. In this regard, we feel that levetiracetam is quite promising as it can be used safely in the presence of liver disease and it can also be given at a high dose quickly and achieves therapeutic levels fast. Availability of an intravenous preparation of levetiracetam now offers significant promise in managing status epileptcus in general and probably in patients with porphyria. Probably, more reports on drug therapy in this situation are needed to improve the literature and confidence in managing this condition. A list of common drugs best avoided in porphyria is given in Table 3.

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The anticonvulsant activity of acetone does not depend upon its metabolites

To the Editors:

Epilepsia recently published a letter (Kalapos, 2007) disputing our conclusions that the anticonvulsant activity of acetone is not mediated by its metabolites (Gasior et al., 2007). The validity of our conclusions was questioned on several grounds, the first of which is that there is a lack of evidence that acetone's metabolites cross the blood–brain barrier. Certainly, for a substance to have anticonvulsant activity, it must enter the brain. We agree with the correspondent that evidence that the metabolites cross the blood–brain barrier is scarce. However, it is certainly not nonexistent. Our own data show that intraperitoneal administration of the metabolites causes dose-dependent changes in seizure threshold and motor impairment, thus providing indirect evidence that these substances are acting on the brain. Moreover, there is direct evidence that orally administered 1,2-propanediol is absorbed and penetrates the blood–brain barrier since the compound can be shown to accumulate in brain tissue by in vivo proton magnetic resonance spectroscopy (Cady et al., 1994). There is also evidence that pyruvate can be transported into the brain by monocarboxylic acid transporters (Nakamichi et al., 2005). Indeed, intraperitoneally administered pyruvate can influence brain injury (Suh et al., 2005; Yi et al., 2007). Measurements of brain methylglyoxal are not available, but the compound is certainly absorbed after oral administration in mice as plasma levels were readily detected (Ghosh et al., 2006).

We should like to emphasize, however, that whether or not the metabolites cross the blood–brain barrier is irrelevant to the conclusion of our report. Our conclusion that the metabolites do not account for the anticonvulsant activity of acetone was based primarily on the finding of a major difference between acetone and its metabolites in their relative activities on two distinct central nervous system-mediated phenomena: acetone raised seizure threshold at markedly lower doses than those that produced motor impairment, whereas this was not the case for the metabolites. This qualitative difference cannot be explained by differences in brain penetration.

Related to this issue, Kalapos also questioned whether intraperitoneal administration of the metabolites was

appropriate, given that they may not cross membranes. Actually, all of the metabolites we tested caused motor impairment, demonstrating that they must be absorbed. In fact, acetol, 1,2-propanediol and methylglyoxal also elevated the seizure threshold (although at higher doses than acetone). Further, Kalapos disputed our purported assertion that acetol failed to demonstrate seizure protection. In fact, we stated that acetol did produce threshold elevations in the pentylenetetrazol model (but not the 4-aminopyridine model), but only at high doses that resulted in marked behavioral impairment not seen with effective doses of acetone. A fourth issue raised was the possible contamination of commercial methylglyoxal. This is certainly a concern and we cannot exclude the possibility that an impurity contributed to the severe toxicity we observed. However, the toxicity is consistent with the known properties of the compound (Choudhary et al., 1997; Kalapos, 1999).

In sum, the results of our study are wholly consistent with the conclusion that the anticonvulsant efficacy of acetone is not dependent upon its metabolites. Whereas acetone was quite potent as an anticonvulsant, equimolar doses of the metabolites did not produce anticonvulsant effects. During ketosis, low millimolar concentrations of acetone are produced, but acetol only reaches low micromolar concentrations and methylglyoxal's concentrations are in the nanomolar range (Beisswenger et al., 2005). Therefore, the metabolites cannot be responsible for the anticonvulsant properties of the ketogenic diet. To be sure, the role acetone plays in the therapeutic efficacy of the ketogenic diet remains to be determined. Nevertheless, there is now abundant evidence that acetone is an effective anticonvulsant in diverse seizure models in rodents (Likhodii & Burnham, 2002; Rho et al., 2002; Likhodii et al., 2003). Further studies are required to define the way in which acetone confers seizure protection.

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NEXT MONTH IN *Epilepsia*

The June issue of *Epilepsia* covers a broad range of topics. The issue begins with a historical piece on Rodriguez-Lafora by Dr. Binder and colleagues, and a critical review about "Seizures in multiple sclerosis" by Dr. Koch and colleagues. Full-length articles deal with such diverse topics as innate immunity in temporal lobe epilepsy, auditory dysfunction in benign rolandic epilepsy, seizures following infection and related to stroke, autonomic consequences of experimentally-induced seizures, issues related to pregnancy and periodicities in women, cortical dysplasia, genetic mutations, and epilepsy surgery in children. Several Letters in Gray Matters focus on *SCN1A* mutations in various populations.

Online Early

Andrade-Valença, "Mesial temporal lobe epilepsy: Clinical and neuropathologic findings of familial and sporadic forms"

Libbey et al., "Seizures following picornavirus infection"

Møller et al., "Balanced translocation in a patient with severe myoclonic epilepsy of infancy disrupts the sodium channel gene *SCN1A*"

Oliva et al., "The diagnostic value of oral lacerations and incontinence during convulsive 'seizures'"

Patil et al., "Is streamlined evaluation of children for epilepsy surgery possible?"

Sakamoto et al., "Autonomic consequences of kainic acid-induced limbic cortical seizures in rats: Peripheral autonomic nerve activity, acute cardiovascular changes, and death"

Takase et al., "Prenatal freeze lesioning produces epileptogenic focal cortical dysplasia"

Tuveri et al., "Reduced serum level of THDOC, an anticonvulsant steroid, in women with perimenstrual catamenial epilepsy"

Uusimaa et al., "Homozygous W748S mutation in the *POLG1* gene in patients with juvenile-onset Alpers syndrome and status epilepticus"

White et al., "The anticonvulsant profile of rufinamide (CGP 33101) in rodent seizure models"

Announcements

1st North American Regional Caribbean Congress

The 1st North American Regional Caribbean Congress on Epilepsy will take place at the Rose Hall Resort and Country Club, Rose Hall, Montego Bay, Jamaica on May 30–31, 2008. The goal of this Congress (A. Ali and R. Fisher, co-chairs) is to provide epilepsy education for medical practitioners in the Caribbean region. Limited space will be available for health professionals from other locations, particularly junior investigators and clinicians. Presentations will cover a broad range of topics, including: Differential diagnosis, EEG, Stigma, AEDs, Pediatric issues, Pregnancy, Neuroimaging, Epilepsy surgery, New treatment options, and specific Caribbean updates. Prospective attendees are encouraged to submit abstracts. This inaugural conference has been made possible by generous support from Novartis, the American Epilepsy Society, and the International League Against Epilepsy. For more information, please contact the Jamaica Epilepsy Association (JEA) at Andrews Memorial Hospital, 27 Hope Rd, Kingston 10, Jamaica, (tel: 876-968-8274), or view the website at http://www.carinar.org

2nd Migrating Course on Epilepsy

The new educational initiative - "Migrating Course on Epilepsy" - is a clinically-oriented course, targeted to specialists at the second and third level of epilepsy care and focused on comprehensive aspects of diagnosis and treatment of epilepsy. The first course was successfully organized in Serbia. The second "Migrating Course on Epilepsy" is planned in close collaboration with the Lithuanian Society for Epileptology, for June 1–8 in Trakai, Lithuania. For more information go to http://www.ilae-epilepsy.org/Visitors/chapters/documents/MigratingCourse2announcement.pdf or http://www.epilepsy-academy.org.

4th Epilepsy Colloquium Erlangen

This international meeting will take place in Erlangen, Germany on June 6–7, 2008. The colloquium will focus on: 1) treatment strategies (including drug monitoring, emergency treatment, new treatment developments), 2) surrogate markers of epileptogenicity, 3) new approaches for quantitative measures of seizure control and neuropsychological function, and 4) study design (e.g., how to test new drugs). For more information, contact Prof. Dr. Hermann Stefan, Epilepsy Center, University Hosptial Erlangen, 6-Schwabachanlage, 91054 Erlangen, Germany; email: Hermann.stefan@uk-erlangen.de or visit http://www.epilepsiezentrum-erlangen.de

9th Eilat Conference on New Antiepileptic Drugs

The 9th EilatConference on New Antiepileptic Drugs will take place June 15–19, 2008, in Sitges, Spain. The program is designed to provide an in-depth progress report on new antiepileptic drugs (AEDs) in different stages of development, as well as to present new findings on second-generation treatments. In addition, sessions will be devoted to: Old and New AEDs in Generalized Epilepsies; Novel Formulations and Routes of Administration of AEDs; Common Targets and Mechanisms of Action of Drugs for the Treatment of Epilepsy and other CNS disorders; and Perspectives on new AED discovery. Conference details can be found at: http://www.eilat-aeds.com under *Forthcoming Conferences*. For more information please contact the Secretariat: Target Conferences Ltd, PO Box

29041, Tel Aviv 61290, Israel, Tel: +972 3 5175150, Fax: +972 3 5175155, e-mail: eilatix@targetconf.com

Advanced International Course: Bridging Basic with Clinical Epileptology

The International School of Neurological Sciences in Venice (ISNV) presents a Summer School Course on Bridging Basic with Clinical Epileptology, on July 28–August 8, 2008, at Venice International University, San Servolo, Venice, Italy. Sponsored by the European Community EPILEARN program, ILAE, EUREPA, and Fondazione Istituto Neurologico Carlo Besta, the Course is designed for PhD students and postdoctoral fellows, to help attendees acquire basic and clinical understanding of the epilepsies, and to critically evaluate the literature and prepare grant applications. Course directors are Marco de Curtis (Italy) and Uwe Heinemann (Germany). Further information is available at http://www.epilepsy-academy.org.

2nd Baltic Sea Summer School on Epilepsy

The 2nd Baltic Sea Summer School on Epilepsy will take place from August 31 - September 4, 2008, close to Copenhagen, Denmark. The deadline for application is June 1, 2008. Please see the EUREPA website http://www.epilepsy-academy.org for further information and the online application form, or contact Petra Novotny at petra@epilepsy-academy.org.

8th European Congress on Epileptology

The 8th European Congress on Epileptology will take place in Berlin, Germany, September 21–25, 2008. It is presented under the auspices of the German and Israeli ILAE chapters. The online abstract submission system will be available late in December 2007. The abstract submission deadline is 14th March 2008. For more information go to: http://www.epilepsyberlin2008.org/.

VIREPA Distance Learning Courses 2008/2009

Four VIREPA e-moderated distance learning courses will start again in October 2008. The courses are: "Genetics of Epilepsy", "EEG in the diagnosis and management of epilepsy", "Neuroimaging" and "Clinical Pharmacology and Pharmacotherapy." An introductory meeting for participants of all courses (not mandatory) will take place during the 8th European Congress on Epileptology in Berlin in September 2008. The deadline for application to all courses is August 1, 2008. For detailed information and application, please see http://ww.epilepsy–academy.org or contact the Epilepsy Academy Office at office@epilepsy-academy.org.

Epilepsy at the Cutting Edge

This international meeting, celebrating the ongoing contributions of Fred and Eva Andermann, will address the genetics of epilepsy and epilepsy surgery. The meeting will be held at the Montreal Neurological Institute and Hospital, Montreal, Canada on October 23–25, 2008. Information is available at http://www.mni.mcgill.ca.

5th Latin American Epilepsy Congress

The 5th Congreso Latinoamericano de Epilepsia will take place in Montevideo, Uruguay on November 5–8, 2008. Jointly sponsored by the ILAE and IBE, the organizing committee is headed by A. Scaramelli (Uruguay), L. Núnez Orozco (Mexico), and S. Moshé (USA). Abstracts are due by May 31, 2008; pre-meeting registration deadline is September 5, 2008. For more information, contact: montevideo@epilepsycongress.org or go to http://www.epilepsymontevideo2008.org/committees.html.

2nd Biennial North American Regional Epilepsy Congress

The American Epilepsy Society will host the 2nd Biennial North American Regional Epilepsy Congress at their 62nd Annual Meeting, 5–9 December, 2008, in Seattle, WA, USA. For more information go to http://www.aesnet.org/go/meetings-and-events/annual-meeting

AES Grants for Innovative, Collaborative Research

The American Epilepsy Society has established a novel grant opportunity that will provide seed support to encourage innovative, collaborative basic or clinical research. Awards from the Research Initiative Fund will be given to AES members who are established investigators. Investigators are encouraged to think "outside the box" and to involve other established investigators who may not be working in the epilepsy field. Letters of Intent are due August 25, 2008. For more information

go to http://www.aesnet.org/go/research/research-awards/research-initiative-awards.

Research Infrastructure Awards Program

The AES and the Epilepsy Foundation are partnering to provide an opportunity for scientists to obtain support for nationwide or international networks of clinical or basic science researchers focused on understanding the causes, consequences and treatment of epilepsy. Multicenter research programs are viewed as important mechanisms through which investigators from around the world can establish centralized databases, common protocols, shared resources, core laboratories and exchange rapidly developing techniques and technologies. The funds are to be used to support pilot projects, and/or to hold organizational and planning sessions. Awards will be given for up to $50,000 per year for two years. Letters of intent are due August 25, 2008. For more information, go to http://www.aesnet.org/go/research/research-awards/research-infrastructure-awards.

Early Career Physician-Scientist Award

The Milken Family Foundation and the American Epilepsy Society announce the call for applications for the Early Career Physician-Scientists awards, open to investigators from around the world. This award is designed to assist physician-scientists embarking on early academic careers devoted to epilepsy research. Preference is given to innovative studies leading to new treatments or other novel translational research. $50,000 USD is awarded for a 12 month period beginning in January 2009. Applications are due by Monday, September 8, 2008. Eligibility requirements and application information are available at http://www.aesnet.org/go/research/aes-sponsored-grant-program.

CALENDAR OF MEETINGS

May 2008

❑ **7th Asian & Oceanian Epilepsy Congress**
15–18 May
Xiamen, China
http://www.epilepsyxiamen2008.org

❑ **1st North American Regional Caribbean Congress on Epilepsy**
30–31 May
Montego Bay, Jamaica
http://www.carinar.org

June 2008

❑ **2nd Migrating Course on Epilepsy**
1–8 June
Trakai, Lithuania
http://www.epilepsy-academy.org/homepage/de/eurepa_activities/current_courses/19.html

❑ **4th Epilepsy Colloquium Erlangen**
6–7 June
Erlangen, Germany
http://www.epilepsiezentrum-erlangen.de

❑ **9th Eilat Conference on New Antiepileptic Drugs**
15–19 June
Sitges, Spain
http://www.eilat-aeds.com

July–August 2008

❑ **Venice Epilepsy Summer School, 7th International Course: Bridging Basic with Clinical Epileptology – 3**
28 July – 8 August
Venice, Italy
email: epilepsysummercourse@univiu.org
http://www.epilearn.eu/summer_course/third/index.html

❑ **2nd Baltic Sea Summer School on Epilepsy**
31 August – 4 September
Copenhagen, Denmark
http://www.epilepsy-academy.org

September 2008

❑ **8th European Congress on Epileptology**
21–25 September
Berlin, Germany
http://www.epilepsyberlin2008.org

November 2008

❑ **5th Latin American Epilepsy Congress (ILAE & IBE)**
5–8 November
Montevideo, Uruguay
http://www.epilepsymontevideo2008.org