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# AES Proceedings

Annual Meeting of the American Epilepsy Society

## December 3, 2005
## Investigators' Workshop
## 2:30 p.m.–5:45 p.m.

**MIW.001**
**Seizures Beget Seizures**
Yehezkel Ben-Ari (INMED Institute, Marseilles, France)

Seizures produce long lasting alterations of the networks that lead to a reduction of the threshold of further seizures. In adults, the underlying mechanisms have been extensively investigated in particular in temporal lobe epilepsies. Seizures notably produced by kainate or pilocarpine induce cell death in vulnerable regions of the hippocampus. This is followed by sprouting and the formation of novel glutamatergic synapses –notably mossy fibres of CA3 pyramidal neurons. These new synapses are functional as attested by the massive rise of glutamatergic EPSCs in target epileptic neurons. Interestingly also recordings from temporal lobe epileptic animals, reveal that these synapses are aberrant since control granule cells use only AMPA receptors mediated synapses whereas after the formation of novel synapses, most EPScs are purely kainate receptor mediated. This implies directly that the sprouting has induced the formation of novel synapses that operate differently from the control ones. Other studies have shown also that the inaugurating status epilepticus induced by the injections of the convulsive agent triggers a cascade of events associated with the activation of hundreds of genes in the hours –days that follow the seizures that are responsible for the sprouting and neo-synapse formation. The period of roughly 3 weeks that follows the seizures is a "silent" period during which seizures are not generally generated and spontaneous events do not take place. Ed Dudek will deal with the events that occur at that stage. One additional basic issue concerns the generation by thalamo- cortical connections of fst oscillations and the role of GABAergic synapses in that event. Mircea Steriade will summarize these events and explain how seizures are generated in the neocortex and how they can affect the network. Finally, relying on the triple chamber that accommodate the intact neonatal hippocampi and their connections, Y Ben-Ari will describe the mechanisms of seizures beget seizures during development. In essence, the questions here are which seizures beget seizures and produce long lasting alterations and which do not. This has important implications as to the determination of the mechanisms at work but also may be useful in a clinical perspective to evaluate potentially deleterious seizures.

**MIW.002**
**Fly, Fish and Worm Models of Epilepsy**
[3]Guy Caldwell, [2]Mark Tanouye, and [1]Scott C. Baraban ([1]Neurological Surgery, UCSF, San Francisco, CA; [2]Environmental Science, UC Berkeley, Berkeley, CA; and [3]Biological Sciences, University of Alabama, Tuscaloosa, AL)

Rodent models of experimental epilepsy have been an especially valuable aid in understanding fundamental aspects of human seizure disorders. While there are distinct advantages to using a rodent model of a human neurological disorder, there is no rationale to support our almost exclusive reliance on this species. Indeed, fundamental research related to genetic modifiers of epilepsy, high-throughput anticonvulsant drug screening and forward-genetic screening strategies to uncover novel epilepsy genes are better suited to simpler systems. Exciting new discoveries in the general field of neurobiology have begun to exploit the experimental advantages of simpler organisms such as C. elegans (worms), Drosophila melanogaster (fruit flies) and Danio rerio (zebrafish). Similar discoveries could be possible in the epilepsy field. To highlight recent advances, an Investigator Workshop is planned to present the current state of knowledge in these systems (and provide a forum to discuss where we can, or should, go from here). Guy Caldwell (University of Alabama) will discuss his work with C.elegans lissencephaly mutants. Using a pentylenetetrazole exposure paradigm, they have uncovered a convulsive phenotype that correlated with interesting intraneuronal deficits in presynaptic GABA vesicle trafficking. This suggests it may be possible to separate the intrinsic neuronal deficits leading to LIS1-dependent epilepsy from the more overt cortical defects associated with neuronal migration. Mark Tanouye (UC Berkeley) will present studies on mutant and wild-type Drosophila tested in a stimulation-induced seizure protocol. Using this approach they have identified "epilepsy" mutants that are especially prone to seizures when compared with normal flies and have begun to explore seizure-suppressor and seizure-enhancer mutations. Scott C. Baraban (UCSF) will discuss his work with zebrafish larvae. Using a PTZ exposure protocol, they have described the electrophysiological, behavioral, pharmacological and molecular aspects of a novel simple vertebrate seizure model. Screening a colony of over 6300 ENU-mutagenized zebrafish, seizure-resistant larvae were identified and are now undergoing further characterization and gene mapping. Jeffrey L. Noebels (Baylor) will act as moderator for a lively discussion of these topics.

**MIW.003**
**Imaging Excitatory Neurotransmission**
[1]Jonathan Wetherington, [2]Ognen Petroff, and [3]Matthias Koepp ([1]Dept of Pharmacology, Emory University, Atlanta, AL; [2]Dept of Neurology, Yale University, New Haven, CT; and [3]Dept of Clinical and Experimental Epilepsy, Institute of Neurology, UCL, London, United Kingdom)

The N-methyl-D-aspartate (NMDA) ion channel plays a role in neuroprotection, neurodegeneration, long-term potentiation, memory, and cognition. It is implicated in the pathophysiology of several neurological and neuropsychiatric conditions. The development of effective radiotracers for the study of NMDA receptors is critical for our understanding of their function, and their modulation by endogenous substances or therapeutic drugs. The intrachannel PCP binding site has attracted most attention, as it is only accessible when the channel is in the active and "open" state", but not when it is in the inactive or "closed" state. The physical location of the NMDA/PCP receptor not only makes it an important theoretical imaging target, but also complicates the development of suitable PET and SPECT radiotracers for this site and attempts to quantify in-vivo binding. An intimate understanding of the biochemical, pharmacological, physiological and behavioral processes associated with the NMDA ion channel is essential to develop improved imaging agents and interpret in-vivo measurements.

This workshop will focus on the development of creative approaches to the study of excitatory neurotransmission in patients with epilepsy using MRI/MRS, PET or SPECT. It will provide participants with an understanding of the biochemical, pharmacological, physiological and behavioral processes associated with the NMDA ion channel and an insight into the difficulties and complexities of imaging excitatory neurotransmission in vivo. The participants of this workshop will discuss the animal and pharmacological models used for in-vitro and in vivo assessment of NMDA receptor functions.

The multi-disciplinary nature of this workshop provides opportunities for interactions between participants and faculty with diverse backgrounds including paediatric and adult neurology/epileptology, basic neuroscience, pharmacology, neurophysiology, neuroradiology and nuclear medicine.

**2.371**

**MODULATION OF HIPPOCAMPAL INTERNEURON EXCITABILITY BY THE ANTIEPILEPTIC DRUG GABAPENTIN**

Biwen Peng, Jason B. Kanske, Kun Zhang, and Russell M. Sanchez (Department of Pharmacology, University of Texas Health Science Center, San Antonio, TX)

**Rationale:** The anticonvulsant mechanism of gabapentin (Neurontin®) has yet to be fully elucidated. Gabapentin increases the hyperpolarization-activated cation current ($I_H$) in hippocampal CA1 pyramidal neurons (Surges, et al., 2003 Epilepsia 44:150), and $I_H$ enhancement in these cells has been proposed to decrease passive conduction of dendritic excitatory postsynaptic potentials (dampening synaptic excitability) by decreasing dendritic membrane resistance (Poolos, et al., 2002 Nat Neurosci 5:767). Notably, $I_H$ also is expressed in hippocampal inhibitory interneurons, and $I_H$ blockade in hippocampal slices was shown to decrease spontaneous inhibitory postsynaptic current (sIPSC) frequency in CA1 pyramidal neurons (Lupica, et al., 2001 J Neurophysiol 86:261). This suggested that $I_H$ activation normally promotes the spontaneous firing of CA1 inhibitory interneurons, perhaps in contrast to its effects on pyramidal neuron excitability. We aimed to determine if, as in pyramidal cells, gabapentin increases $I_H$ in non-pyramidal CA1 interneurons, and whether this effect is associated with increased sIPSC frequency in CA1 pyramidal neurons.

**Methods:** Whole-cell voltage-clamp recordings were obtained from visualized CA1 pyramidal neurons and CA1 s. oriens non-pyramidal neurons in hippocampal slices from P10–17 Long-Evans rat pups. The effects of bath-applied gabapentin (100 $\mu$M) and the $I_H$ blocker ZD 7288 (50 $\mu$M) were examined on $I_H$ recorded from s. oriens interneurons and on sIPSC parameters in pyramidal neurons.

**Results:** $I_H$ was observed in 91% (10/11) of recorded CA1 s. oriens interneurons. Gabapentin significantly increased $I_H$ in 7 of 10 interneurons that expressed $I_H$ within 5–10 minutes of bath application. Analysis of tail-currents indicated that the voltage-dependence of $I_H$ activation was unaltered by the drug. Subsequent application of ZD 7288 completely blocked $I_H$ in all interneurons tested (7/7) regardless of whether prior gabapentin application had increased $I_H$. In CA1 pyramidal neurons, gabapentin significantly increased sIPSC frequencies within 5–10 minutes in 69% (11/16) of cells. ZD 7288 signficantly decreased sIPSC frequency in all cells tested ($n = 7$), and also prevented any change by subsequent combined application of gabapentin and ZD 7288. sIPSC amplitudes and rise times were not altered by either drug.

**Conclusions:** These data indicate that gabapentin can increase $I_H$ in CA1 hippocampal interneurons, similarly to its action in CA1 pyramidal neurons. However, rather than decreasing interneuron excitability, this effect is associated with an increase in spontaneous firing of interneurons, as indicated by increased sIPSC frequency in pyramidal neurons. This increase in basal synaptic inhibition may represent a mechanism by which gabapentin decreases pyramidal neuron synaptic excitability, in addition to its possible direct dampening of dendritic synaptic excitation. (Supported by PHS grant NS 047385 and an EFA Junior Investigator Award.)

**2.372**

**AN INTERNATIONAL MULTICENTER DOUBLE-BLIND RANDOMISED COMPARATIVE TRIAL OF LAMOTRIGINE AND SLOW RELEASE CARBAMAZEPINE IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED EPILEPSY**

[1]Erik Saetre, [3]Emilio Perucca, [4]Jouko I. Isojarvi, [2]Leif Gjerstad, and on behalf of the LAM 40089 Study Group ([1]The Epilepsy Unit, Ullevaal University Hospital, Oslo, Norway; [2]Dept. of Neurology, Rikshospitalet, University of Oslo, Oslo, Norway; [3]Clinical Pharmacology Unit, University of Pavia, Pavia, Italy; and [4]Neurosciences MDC US Clinical, GlaxoSmithKline Research and Development, Triangle Park, NC)

**Rationale:** The objectives of the study were to evaluate the overall effectiveness, safety and tolerability of lamotrigine (LTG) and slow release carbamazepine (CBZ-r) in newly diagnosed elderly epilepsy patients for a 40 week period.

**Methods:** The study used a randomised, double-blind, parallell-group design. Patients aged 65 years or older, who had experienced two or more unprovoked seizures (partial seizures, with/without secondary generalisation, or primary generalised tonic/clonic seizures) were included from five European countries. Excluded were subjects previously treated with any antiepileptic drug for more than 2 weeks in the 6 months prior to randomisation. The patients were randomised 1:1 to treatment with LTG or CBZ-r on a b.i.d. schedule. The dose was escalated over 4 weeks and then adjusted based on efficacy and adverse events. The initial, maintenance and maximum daily doses were 25mg, 100mg and 500mg of LTG, and 100mg, 400mg and 2000mg of CBZ-r, respectively. The duration of the maintenance phase was 36 weeks.

**Results:** Of 184 randomised subjects 93 received LTG (46 males = 49%) and 91 received CBZ-r (56 males = 62%). Mean age was 74.3 years (SD6.2) vs. 73.1 years (SD5.5) in the two treatment groups, respectively. In the LTG group, 68 of 93 subjects completed the study (73%), compared to 61 of 91 (67%) in the CBZ-r group ($p = 0.33$). Time to first seizure was shorter in the LTG group in the Per Protocol analysis set (25% fractile in the survival curve: 8.4 weeks on LTG vs. 19.3 weeks on CBZ-r, $p = 0.022$); however the difference was not significant in the Intention to Treat (ITT) set, using the log-rank test. The proportion of seizure-free subjects in the 4 to 40 week treatment period, not accounting for subjects withdrawn before week 4, were 53 of 87 (61%) on LTG, and 68 of 90 (76%) on CBZ-r ($p = 0.036$). The number of subjects seizure-free from week 20 to week 40, after excluding from the analysis those who withdrew before week 20, was 53 of 75 (71%) for the LTG group and 59 of 69 (86%) for the CBZ group ($p = 0.032$). The number of individuals who experienced adverse events (AE) did not differ in the two groups. The number of AEs leading to stop permanently of the treatment was 23 (25%) on CBZ-r compared to 13 (14%) on LTG. There was no difference in AEs being judged to be related to the study drug by the investigator.

**Conclusions:** With the treatment schedules investigated in this study, CBZ-r produced greater seizure-freedom rates, whereas LTG tended to be associated with lesser AE-related withdrawals. Retention on treatment was comparable in the two groups. (Supported by GlaxoSmithKline (LAM 40089).)

**2.373**

**EFFECT OF AGE AND GENDER ON THE PHARMACOKINETICS OF ESLICARBAZEPINE ACETATE**

Patricio Soares-da-Silva, Luis Almeida, Amilcar Falcao, and Joana Maia (Research and Development, BIAL, S Mamede do Coronado, Porto, Portugal)

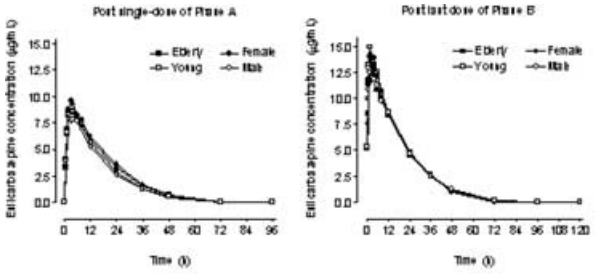
**Rationale:** Eslicarbazepine acetate is a novel voltage-gated sodium channel blocker in development for the treatment of epilepsy, bipolar disorder and neuropathic pain. The objective of this study was to determine the effect of age and gender on the pharmacokinetics of eslicarbazepine acetate.

**Methods:** Single-centre, open-label, parallel-group study in 12 young (18–40 years) and 12 elderly (65 or over) healthy subjects. In each age group, 6 subjects were female and 6 were male. The study consisted of a single-dose (600 mg) period (Phase A) and a multiple-dose (600 mg, once-daily, for 8 days) period (Phase B), separated by 4 days.

**Results:** Eslicarbazepine acetate was extensively metabolized to eslicarbazepine (S-licarbazepine), the main active metabolite. Plasma concentration-time profiles of eslicarbazepine following the single-dose of Phase A and the last dose of Phase B are presented in Figure 1. Following a 600 mg single-dose, mean maximum eslicarbazepine plasma concentrations ($C_{max}$) and area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) were respectively 9.9 $\mu$g/mL and 180.9 $\mu$g.h/mL in young subjects, and 9.5 $\mu$g/mL and 196.0 $\mu$g.h/mL in elderly subjects, and respectively 9.3 $\mu$g/mL and 171.9 $\mu$g.h/mL in male subjects, and 10.1 $\mu$g/mL and 205.0 $\mu$g.h/mL in female subjects. After multiple-dosing, steady-state plasma concentrations were attained at 4 to 5 days of administration in both age and gender groups, consistent with an effective half-life in the order of 17–18 hours**.** Post last dose of Phase B, mean $C_{max}$ and $AUC_{0-\infty}$ of eslicarbazepine were respectively 17.3 $\mu$g/mL and 296.7 $\mu$g.h/mL in young subjects, and 15.1 $\mu$g/mL and 294.3 $\mu$g.h/mL in elderly subjects, and respectively 15.5 $\mu$g/mL and 295.8 $\mu$g.h/mL in male subjects, and 16.8 $\mu$g/mL and 295.2 $\mu$g.h/mL in female subjects. Following single-dose, the eslicarbazepine $C_{max}$, $AUC_{0-24}$ and $AUC_{0-\infty}$ elderly/young geometric mean ratios (GMR) and their 95%

confidence intervals (95%CI) were 0.95 (0.81, 1.14), 1.02 (0.86, 1.24) and 1.06 (0.88, 1.32) and the female/male GMR (95%CI) were 1.09 (0.87, 1.43), 1.16 (0.95, 1.48) and 1.17 (0.90, 1.63), respectively. Following last dose, the eslicarbazepine $C_{max}$, $AUC_{0-24}$, and $AUC_{0-\infty}$ elderly/young GMR (95%CI) were 0.88 (0.77, 1.03), 0.98 (0.90, 1.09), and 1.01 (0.89, 1.18) and the female/male GMR (95%CI) were 1.10 (0.98, 1.27), 1.04 (0.88, 1.28), and 1.01 (0.83, 1.30), respectively.

**Conclusions:** The pharmacokinetic profile of eslicarbazepine acetate was not affected either by age nor gender.




Eslicarbazepine plasma concentration-time profile following a 600 mg single dose and following the last dose of a 8-day once-daily 600 mg dose of eslicarbazepine acetate

**2.374**

**SEIZURE FREEDOM IN NEWLY DIAGNOSED PATIENTS WITH PARTIAL SEIZURES RECEIVING OXCARBAZEPINE AS MONOTHERAPY**

Monique Somogyi, and Kevin McCague (US Clinical Development & Medical Affairs, Novartis Pharmaceuticals, East Hanover, NJ)

**Rationale:** Seizure freedom is the primary goal in the treatment of patients with epilepsy over the long term. Seizure freedom 1–2 days after initiation of monotherapy with oxcarbazepine (OXC) in patients with partial seizures remaining seizure free throughout 56 weeks of treatment was assessed in a subanalysis of two clinical trials.

**Methods:** The efficacy and safety of monotherapy with OXC compared with phenytoin (PHT) in adults (16–63 years) (Bill et al. Epilepsy Res 1997) and children (5–18 years) (Guerreiro et al. Epilepsy Res 1997) with newly diagnosed seizures was evaluated in two multicenter, double-blind, randomized, parallel-group clinical trials. During a 8-week titration period in both studies, OXC was initiated at 300 mg/day (adults) and 150 mg/day (children) and PHT at 100 mg/day (adults) and 50 mg/day (children) and titrated to a maximum dose of OXC 2400 mg/day and 800 mg/day PHT. After the titration periods, patients were maintained on their maximum tolerated dose during a 48-week maintenance period. Seizure freedom rates for patients with seizures at baseline who were seizure free at days 1 and 2 of treatment and remained seizure free for the duration of double-blind treatment were assessed. Adverse events (AEs) for this subset of patients were also tabulated.

**Results:** For adults seizure free at Days 1 & 2 who remained seizure free throughout the double-blind period, the mean age was 29 years for both groups, and the baseline partial seizure rate/28 days was 1.5 and 2.9 for the OXC and PHT groups, respectively. For the same subset of children, the mean age was 10 and 11 years and the baseline partial seizure rate/28 days was 1.8 and 2.7 for the OXC and PHT groups, respectively. Seizure freedom rates are presented in Table 1.

In adults, 1 (3%) and 2 (6%) of OXC- and PHT-treated patients, respectively, discontinued due to AEs. One PHT-treated patient died during the study. The most common (≥20% of patients) AEs in the OXC-treated patients were headache, somnolence, viral infection, dizziness, nausea, and vomiting. In children, 1 (3%) and 3 (9%) of OXC- and PHT-treated patients, respectively, discontinued due to AEs. The most common (≥20% of patients) AEs in the OXC-treated patients were headache, somnolence, viral infection, and fever.

**Conclusions:** The majority of adults and children with newly diagnosed partial seizures initiated with OXC monotherapy and seizure free at Days 1 & 2 of treatment remained seizure free for more than 1 year.

**Table 1. Number (%) patients seizure-free at Days 1 & 2 of treatment and who remained seizure-free throughout the double-blind period**

| | OXC | | PHT | |
|---|---|---|---|---|
| | Seizure-free at Days 1 and 2 | Seizure-free throughout double-blind period | Seizure-free at Days 1 and 2 | Seizure-free throughout double-blind period |
| Adults with newly diagnosed seizures | N=77<br>60 (78) | N=60<br>37 (62) | N=85<br>64 (75) | N=64<br>33 (52) |
| Children with newly diagnosed seizures | N=65<br>58 (89) | N=58<br>40 (69) | N=64<br>50 (78) | N=50<br>34 (68) |

Overall, OXC was safe and well tolerated. (Supported by Novartis Pharmaceuticals.)

**2.375**

**RETIGABINE DECREASES BEHAVIORAL AND ELECTROGRAPHIC SEIZURES IN THE LAMOTRIGINE- RESISTANT AMYGDALA KINDLED RAT MODEL OF PHARMACORESISTANT EPILEPSY**

Ajay K. Srivastava, and H. Steve White (Antiepileptic Drug Development Program, Department of Pharmacology and Toxicology, Salt Lake City, UT)

**Rationale:** We have previously reported that the lamotrigine (LTG)-resistant amygdala kindled rat displays resistance to carbamazepine, phenytoin and topiramate, but not valproate (Srivastava et al., Epilepsia 2003).

This animal model may provide a unique system to evaluate novel antiepileptic drugs (AEDs). Since 1993 nine new AEDs have been introduced for the treatment of epilepsy. Although effective for the treatment of partial epilepsy none of these drugs have led to a significant reduction in the prevalence of refractory epilepsy.

Recently the broad spectrum AED, retigabine (RGB) has been found to be effective in suppressing refractory epileptiform discharges in vitro in combined hippocampal-entorhinal brain slices (Smith-Yockman et al., Epilepsia 2004, Armand et al., Epilepsia, 2000). RGB is unique among the AEDs because of its ability to enhance the M current through a shift in the activation kinetics of KCNQ2/3 channels. The present study was undertaken to assess the ability of retigabine (RGB) to block both behavioral and electrographic seizures in LTG-resistant amygdala kindled rats.

**Methods:** Two groups of male Sprague Dawley rats were kindled via amygdala stimulation (Postma et al., Epilepsia, 2000). One hour before each kindling stimulation, rats in the control group received 0.5% methylcellulose and rats in the experimental group received LTG (5mg/kg, i.p.). Treatments were stopped once the control group were fully kindled. One day later, both groups were challenged with a higher dose of LTG (15 mg/kg, i.p.) to verify LTG- resistance in the experimental group (i.e., LTG- pretreated rats). The efficacy of RGB (10, 20 and 40 mg/kg administered 10 min prior to kindling stimulation) was then evaluated in both experimental groups.

**Results:** A stable (stage 4–5) kindled state was established in both vehicle- and LTG-treated animals over a period of 17–18 days. Upon subsequent challenge with a higher dose of LTG, the fully kindled seizure of the vehicle-treated rats, but not the LTG-treated rats, was blocked by LTG. RGB (10, 20, and 40 mg/kg) displayed a dose-dependent anticonvulsant effect in both LTG-sensitive and LTG- resistant animals. Specifically, RGB blocked the expression of the behavioral seizure and decreased the after-discharge duration in both groups.

**Conclusions:** The present findings suggest that RGB is highly effective in LTG-resistant animal model of drug resistant epilepsy. These results support further clinical development in patients that are refractory to both first and second generation antiepileptic drugs. These findings also suggest that the LTG-resistant, amygdala-kindled rat may represent a novel model of pharmaco-resistant epilepsy. Ongoing studies continue to evaluate the mechanism underlying the development of