

Society proceedings

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- 1 Changes in muscarinic receptor mRNA after seizures do not correlate with changes in receptor protein levels — Nancy Mingo¹, Sesath Hewapathirane¹, James H. Eubanks^{1,2}, and W. McIntyre Burnham¹ (¹University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada, ²Toronto Western Hospital, Toronto, Ontario, Canada)**

Past studies have reported many short- and long-lasting changes in the expression of mRNA following seizures. Past studies from our own laboratory have reported decreased expression of mRNA for m1 and m3 muscarinic cholinergic receptors in the hippocampus following seizures. These changes have been found after 5 Stage 5 amygdala-kindled seizures, 8 electroconvulsive shock (ECS) seizures, or five minutes of a kainic-acid induced seizure.

The present study was designed to determine whether these changes in m1 mRNA translated into changes in receptor protein. Rats were given 5 Stage 5 amygdala-kindled seizures, 8 electroconvulsive shock seizures, or five minutes of a kainic-acid induced seizure. Twenty-four hours later, there were sacrificed, and Western blots were made and analyzed. It was found that the changes in mRNA levels were not paralleled by changes in immunoreactive proteins. No changes in m1 receptor mRNA were found 24 h after kindled, kainic acid or ECS seizures.

In the muscarinic system, changes in receptor mRNA can occur without changes in receptor protein. These results call into question the significance of the many post-seizure changes in mRNA that have been reported in past studies.

- 2 Seizure like events in isolated hippocampal slices from fragile X mental retardation protein knock-out mice — Chris Feeney¹, Shanthini Mylvaganam¹, Miron Derchansky^{1,2}, Peter L. Carlen^{1,2} (¹Toronto Western Research Institute, Depts. of Medicine (Neurology) and Physiology, Toronto, Ontario, Canada, ²University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada)**

Fragile X syndrome is the most common inherited form of mental retardation, affecting 1 in 1200 males and 1 in 2500 females. The condition is a result of the loss of expression of the Fragile X Mental Retardation Protein (FMRP). This syndrome is

characterized by variable intellectual impairment, hyperactivity, autistic-like behaviors, anxiety and seizures (up to 40% of patients). Using FMRP knock-out mice (FMRP-KO), we have explored the propensity of isolated hippocampal slices to display seizure-like-events (SLE) in response to low-Mg perfusate and recurrent tetanizations. Approximately 20% of slices from FMRP-KO mice exhibited spontaneous bursting whereas this was not seen in slices from wild type mice. In low-Mg perfusate, a higher percentage of slices from FMRP-KO showed SLEs than wild type mice (75% vs. 40%), and the onset to the first SLE event was significantly reduced as compared to wild type mice (< 10 min vs. > 25 min). In normal perfusate, 2 or 3 episodes of 100 Hz tetanizations (2 s, every 10 min) were sufficient to induce SLEs in a majority of slices from FMRP-KO mice. In contrast, slices from wild type mice hippocampi could rarely be provoked into SLEs following up to 6 tetanizations, and less than half of these slices exhibited SLEs with a subsequent 30 min exposure to low-Mg perfusate. Initial results using the mGluR5 receptor antagonist, MPEP, showed no anticonvulsant effects in KOs or controls in low-Mg perfusate. This in vitro seizure model provides a robust phenotype to research the neurobiology of the Fragile X syndrome.

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- 3 The acetone hypothesis: what evidence do we have supporting the idea that acetone is the anticonvulsant mechanism of the ketogenic diet? — Kirk J. Nylen¹, Sergei S. Likhodii¹, and W. McIntyre Burnham¹ (¹University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada)**

The anticonvulsant mechanism of the ketogenic diet (KD) is currently unknown. Studies from our laboratory suggest that acetone may play a major role. We demonstrated that the KD does not appear to have significant anticonvulsant actions in rats unless extremely sensitive threshold tests are used. We have also shown that rats on the KD do not have significantly elevated blood-acetone concentrations. Control rats tend to have acetone concentrations ranging from 0.05–0.15 mM. Rats fed a KD have blood-acetone concentrations between 0.1–0.2 mM. Although control levels in humans are similar to those seen in rats, humans on the KD develop blood-acetone concentrations ranging from 1 mM to 10 mM. These concentrations are sufficient to demonstrate significant, broad-spectrum anticonvulsant effects in several seizure preparations (e.g. kindling, maximal electroshock,

subcutaneous pentylenetetrazole and AY-9944) in rats. We hypothesize that anticonvulsant effects of the KD in rats were not observed due to the “subtherapeutic” concentrations of blood-acetone. We further hypothesize that the KD has broad-spectrum anticonvulsant effects in children on the KD because these children develop “therapeutic” levels of acetone. Research exploring these hypotheses is currently underway.

4 Inhibition of seizure-like activity induced by hypoglycemia protects against hypoglycemic cell death — Peter A. Abdelmalik^{1,2}, W. McIntyre Burnham¹, and Peter L. Carlen^{1,2} (¹University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada, ²Toronto Western Research Institute, Toronto, Ontario, Canada)

The threat of severe hypoglycemia makes the goal of tight glycemic control in patients suffering from type one diabetes mellitus very difficult. Severe hypoglycemia, which can result in seizures and coma, has been shown to have irreversible consequences on neuronal function and survival. Especially vulnerable areas are the dentate gyrus and CA1 of the hippocampus, which may explain some of the cognitive deficits associated with severe hypoglycemia. Using extracellular field recordings in the immature, intact mouse hippocampus, we have devised an *in vitro* model of hypoglycemic seizures in which neuronal specific cell death is confined to the CA1 and dentate gyrus areas of the hippocampus, similar to what has been described *in vivo*. NMDA and AMPA/kainate antagonists prevented both hypoglycemic cell death and hypoglycemic seizure activity. The clinical anticonvulsants phenytoin (20 μ M) and valproate (1 mM) did little to prevent hypoglycemic seizures and cell death. However, the GABAergic agonist midazolam (10 nM) was effective in preventing both hypoglycemic seizures and cell death. These data support the hypothesis that hypoglycemic neuronal damage is greatly exacerbated by seizure-like activity and excessive glutamatergic activation.

5 Close returns: from EEG to network models and back again — Elan Liss Ohayon^{1,2}, Paul A. Hwang^{1,2}, Paul W. Tsang³, Hon C. Kwan³, and W. McIntyre Burnham^{1,2} (¹University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada, ²Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada, ³Department of Physiology, University of Toronto, Toronto, Ontario, Canada)

Previously we have shown how nonlinear methods, such as close return analysis, can be used to categorize neural dynamics in healthy and epileptiform EEG recordings. Here we demonstrate that these algorithms can be similarly applied to categorizing activity in computer models. In particular, we apply these forms of analysis to both random networks and layered networks with near-neighbour connectivity. The assessments have helped suggest several important principles:

(1) The pitfalls of ubiquitous synchrony: The modeling and analysis have demonstrated that periodic dynamics are often the

most common regime. This finding questions the popular notion that synchrony and the purported “binding problem” are key to understanding cognition. In fact, the prevalent tendency of the models to fall into – and get trapped in – oscillatory phase-locked synchrony suggests that synchrony might be more of a pathological problem than a cognitive asset. An inability to process or interact with the world under the synchronous state, as seen in embodied models, suggests that the central issue may actually be an “unbinding problem.”

(2) Intermittency mechanisms: Categorizing dynamics in random models has helped uncover hitherto unconsidered mechanisms for intermittent ictal events. These forms of intermittency do not require ongoing changes to network properties or external perturbation. The autonomous switching between dynamical categories of neural activity may help explain some of the most fundamental mechanisms of epilepsy and attention.

(3) Network structure and boundaries: Categorizing dynamics and relating these to changes in spatial structure has highlighted the fact that localized alterations in architecture, such as lesions, can result in massive changes to network dynamics even in the absence of intrinsic changes to cell properties.

Conclusions: The application of these non-linear forms of analysis to models has allowed us to consider the interrelation of network structure, constituent unit properties, emergent neural dynamics and embodied interaction with the world. The findings offer novel ways of understanding collective dynamics and the manner in which these might explain ictal activity. The models thus forward conceptual possibilities, specific hypotheses and potential mechanisms that can now be tested in the clinical setting.

6 Which frequencies — for what purpose? — E. Rodin¹, M. Funke¹ (¹Department of Neurology, University of Utah)

Digital technology has greatly expanded the opportunities for evaluating the entire cerebral electro-magnetic frequency spectrum. Data can be acquired from DC to several kHz and subsequently filtered for whatever frequency band one desires to study. Sub-delta frequencies (0.1–1 Hz) can be easily separated from ultra-fast activity, above 100 Hz, in the same recording, and their relative contributions to a patient’s illness assessed. What may be regarded as artifact can in some instances be demonstrated to be of cerebral origin when the data are appropriately filtered and amplified.

The past decade has seen a resurgence of interest in faster frequencies and various designations have been applied. It will be shown that, in some epilepsy patients, bursts of fast frequencies, when recorded on conventional filter settings (1–70 Hz), represent attenuated activity between 100–300 Hz. The bursts are similar to what the senior author reported in a series of papers during the 1970 s in experimental animals. While focal spike discharges are best seen with filter settings between 3 and 45 Hz, ultra-fast bursts become apparent when frequencies below 70 Hz are eliminated. They do not necessarily occur in conjunction with spikes, can have different topographies, but do appear to be relevant for cortical epileptogenesis.

The clinical correlations of sub-delta activity are more difficult to ascertain unless structural lesions are present. In their absence sub-delta activity seems to be related mainly to autonomic CNS

functions. Relevant examples from electrical and/or magnetic data will be shown.

7 The Electrocerellogram — Ernst Niedermeyer, MD¹ (Sinai Hospital, The Johns Hopkins University, School of Medicine and Hospital, Baltimore, MD)

At the 2001 meeting of this association, we stressed (with Sherman) the significance of ultrafast EEG recordings with digital methodology. On the other hand, as early as 1935, Adrian reported 150–250/sec activity in the cerebellum of the cat and, in the following years, excellent experimental studies confirmed Adrian's findings. In addition to ultrafast activity, there were also slower frequencies down to the delta range. How was this possible? By photoregistration using bromide silver paper.

While the introduction of EEG instruments with ink-writing pens permitting long-time tracings was most warmly welcomed by the clinical EEG community, the loss of the ultrafast range evidently hurt the experimenter, but did not concern the clinical electroencephalographer. Personal work (with Uematsu, 1974) in human epileptics with the use of depth leads in the fastigial and dentate nuclei (inserted for therapeutic stimulation) showed unexpected invasion of epileptic activity into the cerebellum, but was hampered by the inability to record the ultrafast range. The stimulations were clinically unsuccessful.

The cause of predominant ultrafast activity in the cerebellar cortex and nuclei is still unknown.

8 Post-ictal forceful yawning in a patient with nondominant hemisphere epilepsy: a case study — Alexei Yankovsky¹, Frederick Andermann¹, François Dubeau¹ (Department of Neurology and Neurosurgery, Montreal Neurological Hospital and Institute, McGill University, Montreal, Quebec, Canada)

Background: Yawning has surprisingly rarely been described in association with seizures and has not previously been documented by video-EEG.

Methods: We studied a 48-year-old woman with a long history of non-dominant centro-parietal seizures who developed forceful repetitive post-ictal yawning.

Results: The patient began having intractable epileptic attacks at age 18. She described five types of seizures. At 30, she underwent invasive EEG studies, which showed epileptiform abnormalities over the right parietal operculum. Brain CT and MRI were normal. A right inferior parietal and posterior temporal resection did not lead to improvement. At 31, she had a second resection at the temporal edge of the previous operation again with no improvement. The tissue showed no definite abnormality. Yawning appeared late (approximately 24 years after onset of her seizures). It was repetitive, irresistible and forceful starting from 1 to 30 s after the seizure offset and lasting from 5 to 60 s. It was observed after most (86%) focal sensory-motor seizures and after one third of simple sensory attacks. She was alert during all yawning episodes.

Conclusions: Yawning may preferentially involve the non-dominant hemisphere and, therefore have lateralizing value similar to induction of other autonomic peri-ictal symptoms such as spitting, water drinking, vomiting, urinary urgency or coughing.

9 Wicket activity does not indicate the presence of epilepsy — Gregory Krauss, MD¹, Amy Abdallah, BS¹, Ronald Lesser, MD¹, Richard E. Thompson, PhD², and Ernst Niedermeyer, MD³ (The Johns Hopkins University, School of Medicine and Hospital, Baltimore, MD, ²Department of Biostatistics, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD, ³Sinai Hospital, Baltimore, Maryland)

Objective: EEG wicket spikes are brief, prominent, medium to high voltage temporal discharges, and wicket rhythms are 6–11 cps medium to high voltage bursts that are sometimes misidentified as epileptogenic activity. We identified patients with wicket activity referred to our Center for evaluation and treatment of epilepsy.

Methods: We re-read EEGs for patients referred for epilepsy management and identified patients with wicket activity. We compared the clinical and EEG features of these patients to age and gender-matched patients with partial-onset epilepsy using univariate and multivariate analysis.

Results: The majority (54%; 25/46) of patients with wicket activity had EEGs which previously had been interpreted as showing epileptogenic patterns and the patients had been incorrectly diagnosed to have epilepsy. Several features distinguished patients with misdiagnosed epilepsy ($N=25$) from patients with epilepsy ($N=25$): mid-adult ages of onset of episodes (mean 38.4 years versus 19.8 years), prolonged clinical episodes (mean 155 min versus 2.3 min), and long duration of EEG wicket or spike patterns (mean 0.66 s versus 0.11 s). After controlling for other factors, patients with major confusion during episodes were more likely to have epilepsy than non-epileptic episodes.

Conclusion: Electroencephalographers should be aware of this EEG pattern and should educate general neurologists regarding it, so that they will be cautious about misinterpreting wicket patterns as epileptogenic, particularly in patients with clinical episodes atypical for epilepsy. When questions arise regarding the significance of a given pattern, additional EEG recording should be obtained.

10 Hyperphosphatasia with neurologic deficit: EEG and evoked potential studies in a case with a pyridoxine-responsive seizure disorder — Miles D. Thompson^{1,2,7}, Annie Killoran^{1,5}, Marjan Nezarati⁴, David E.C. Cole^{1,3,4}, and Paul A. Hwang^{6,7} (Departments of Laboratory Medicine and Pathobiology¹ and Pharmacology², University of Toronto, Toronto, Ontario, Canada ³Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada, ⁴Department of Medical Genetics, Hospital for Sick Children, Toronto, Ontario, Canada, ⁵Department of Medicine, University College, Dublin, ⁶Department of Neurology, North York General Hospital, Toronto, Ontario, Canada, ⁷University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada)

We review the EEG and evoked potential findings characteristic of infants with seizure disorders responsive to pyridoxine. Of particular interest are the differential neurological findings associated with pyridoxine-responsiveness in genetic deficiency of serum alkaline phosphatase activity (hypophosphatasia) and a

rare form of inherited alkaline phosphatase excess or hyperphosphatasia. In this context, we report a case of pyridoxine-responsive hyperphosphatasia characterized by developmental delay and tonic-clonic seizures associated with persistently elevated alkaline phosphatase and low serum pyridoxal 5'-phosphate, known as hyperphosphatasia with neurologic deficit (MIM #239300). The low serum levels of pyridoxal 5' phosphate (6 nmol/L; normals >20 nmol/L) prompted the use of a diagnostic pyridoxine-EEG challenge (100 mg as two IV bolus injections), which induced a paradoxical response suggestive of stage 3 or 4 slow-wave sleep. With institution of daily pyridoxine supplements (100 po) and withdrawal of phenobarbital, seizures have not been evident. Normal visual, auditory and sensory evoked potentials contrast with those found in other pediatric seizure disorders. The importance of pyridoxine challenge in clinical assessment of inherited disorders of alkaline phosphatase metabolism with neurological features is emphasized.

11 Use of EEG biofeedback for emotional stabilization — Sarala Devi, MD¹, Paul Gunser, PsyD¹, and Susy Mendes, BA, MA Candidate¹ (¹St John's Riverside Hospital, Yonkers and the Community Hospital, Dobbs Ferry, NY, New York, ²John Jay College of Criminal Justice, City University of New York, New York)

This is a case study of a 56-year-old female patient status post MVA seen by both authors. Dr Devi performed a comprehensive neurological evaluation and had the patient evaluated with a Video EEG to rule out seizure disorder. The patient was receiving EEG Biofeedback with a BioComp EEG as well as prior thermal biofeedback and Heart Rate Variability Biofeedback to reduce her Post Traumatic Stress Disorder symptomology of increased anxiety and panic experiences as well as essential tremors. EEG electrode placement using the standard 10–20 placement format was limited to Cz with bilateral ear (reference and ground) placements as well. HRV monitoring was performed with a Heart Math HRV monitor placed on the left index digit. Temperature probe placement was administered on the right index digit if the left was used for HRV monitoring.

Although Dr Devi placed the patient on Topomax, biofeedback as mentioned previously was administered to this patient. Over a three-month period, small increases in Alpha waves were noted while Theta was reduced. Subjective Anxiety experiences were lessened and Tremors reduced substantially as observed by one of the authors (Dr Gunser) and the patient.

Further evaluation of the efficacy of EEG Biofeedback for anxiety and Tremors needs to be explored. An extension of this study should be undertaken with a sample of several patients (Table 1).

Table 1
EEG wave activity in a patient status post-MVA over a 3-month period

	9/15/04	10/21/04	11/04/04	12/6/04	12/13/04	Overall means
Mean A EEG theta	7.16	10.14	10.49	11.87	8.98	9.728
Mean A EEG alpha	9.38	10.07	11.41	10.05	12.03	10.588
Mean A EEG SMR	3.78	5.38	5.82	5.77	4.72	5.094
Mean A EEG Lbeta	5.17	5.94	6.36	6.75	6.71	6.186
Mean A EEG HbETA	5.53	8.16	6.75	10.89	7.98	7.862