Clinical Neurophysiology 124 (2013) e5–e8

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Society Proceedings

Eastern Association of Electroencephalographers, 65th Annual Meeting, New York, February 18–19, 2011

1. The anticonvulsant effects of n-3 PUFA: Animal studies—Marc Olivier Trepanier, Ameer Taha, Richard Bazinet, McIntyre Burnham (The University of Toronto, Toronto, Ont., Canada)

The omega-3 polyunsaturated acids (n-3 PUFA) show great promise as a therapy for epileptic seizures. There has been considerable confusion, however, in the animal data related to the n-3 PUFAs' anticonvulsant effects. Our own recent work has clarified this confusion, and led to a simple, reproducible animal preparation in which to study the n-3 PUFAs' mechanism(s) of action.

We first attempted to replicate the studies of Yehuda et al. (1994), who had reported dramatic seizure suppression after 21 days of 40 mg/kg injections of the "SR 3" formula i.p in rats. In our replication, we found *no* effect at all at this dose (Taha et al., 2006). We therefore tested the higher dose of 200 mg/kg of the SR-3 mixture. At 200 mg/kg, we found a significant increase in PTZ seizure latency, although no change in severity (Taha et al., 2009).

We subsequently tried acute administration of a single dose in rats, switching from SR 3 to docosahexaenoic acid (DHA). Injecting subcutaneously (s.c.), we found a significant elevation in PTZ-seizure latency following after a single injection (Taha et al., 2010). Our dose–response curves in this study, however, were "inverted U" shaped.

In parallel studies, we tested dietary (p.o.) administration. Working in rats with chronically implanted electrodes, we found that dietary PUFAs elevated thresholds in both the cortex and the amygdala of rats. These effects, however, took several months to occur (Taha et al., in preparation).

To simplify the kinetics, we have moved to intravenous (i.v.) injections of DHA (tail vein in rats). Our i.v. experiments have now shown anticonvulsant effects 5 min after injection and plasma concentrations that rise rapidly, plateau at 5 min, and drop to baseline a minute after infusion (Trepanier et al., in preparation). We have therefore finally evolved a preparation in which anticonvulsant effects and plasma concentrations parallel the known kinetics of DHA. This preparation will now allow a meaningful study of DHA's mechanisms of anticonvulsant action.

doi:10.1016/j.clinph.2012.08.029

2. Fetal alcohol spectrum disorder: Epilepsy and neuropsychiatric disorders—Michael Sumner, Stephanie Bell, Paul A. Hwang (Neuropsychiatry Consultant, Queen's University, Kingston, Ont., Canada, North York General Hospital, University of Toronto Epilepsy Research Program (UTERP), Toronto, Ont., Canada)

The Fetal Alcohol Syndrome (FAS) is a congenital disorder due to prenatal exposure to alcohol, leading to a dysmorphic infant: microcephaly, developmental delay and often seizures. Many offspring at risk are non-dysmorphic, referred to as Fetal Alcohol Spectrum Disorder (FASD), including possible and probable FAS and FRND, requiring high diagnostic acumen.

Aim: A retrospective analysis of 400 cases of FAS, FASD and FRND revealed an unexpectedly high incidence of seizure disorder in 20%, including frequent epileptic seizures in 12% (Bell et al. ACER 2010). The current study examines a cohort for neuropsychiatric difficulties encountered in the management of these adolescents and adults ($N = 10$).

Methods: Only those subjects that came to medical attention and/or psychosocial intervention had detailed neuropsychiatric assessment. Hence there is a bias towards over-estimating the prevalence of neuropsychiatric difficulties. They were all examined by the same neuropsychiatrist (MGS), had EEG recorded with electrodes in the 10–20 system plus zygomatics, almost always with sleep: spontaneous, after sleep-deprivation or overnight polysomnographic recording with video-EEG in a sleep lab. All EEGs were read blind by the same board-certified clinical neurophysiologist (PAH). Representative subjects are reviewed.

Results: In addition to a high prevalence of seizure disorder (approximately 10 times normal), recurrent afebrile unprovoked seizures (epileptic) were found in 12% of the study cohort (>10 × normal), requiring long-term follow-up and treatment with AEDs appropriate for the seizure types: CBZ, OxCBZ, VPA, LMT or TPM. Breakthrough seizures require (BZDs) benzodiazepines for acute management, loading doses of PHT and/or PB for status epilepticus. Neuropsychiatric issues included attention deficit +/− hyperactivity, mood instability, dysprosody and depression, often responding to the same AEDs as above, plus SSRI or antipsychotics. The adolescents experienced learning difficulties in school and/or at work, requiring cognitive behavior therapy, speech therapy and possibly EEG biofeedback.

Conclusion: The FASD is associated with increased seizure risk, learning disorder, neuropsychiatric difficulties that require further intervention. Whether these are due to developmental cerebral dysgenesis, neurotoxicity of ethanol or metabolites in utero, or sequelae of postnatal traumatic brain injuries, vitamin deficiency or a disorder in brain metabolism as a result of epigenetic response to a hostile neural environment, remains to be determined in future studies.

doi:10.1016/j.clinph.2012.08.030

3. Perisaccadic EEG components in Parkinson disease patients—M.A. Javaid, A. Lafontaine, S. Glazman, I. Bodis-Wollner [1] (SUNY Downstate Medical Center, 450-Clarkson Avenue, Brooklyn, NY 11203, USA)

Background: Perisaccadic gamma power modulation is impaired for voluntary saccades (Forgacs et al., 2008) in Parkinson disease (PD) patients.

Purpose: To quantify both perisaccadic gamma (PG) and beta PB components of the EEG in PD.

Method: We quantified the anterior–posterior distribution of PG (35–45 Hz) and PB (18–24 Hz) range EEG in PD patients while they executed voluntary saccades, towards and away from their body–centers/central fixation.

The EEG was recorded with Electro-cap over frontal, parietal, occipital and temporal scalp sites in 14 healthy subjects (age 55–72 yrs, 6 females) and in 11 PD patients (age 57–78 yrs, 5 females, H-Y stage 1–3). EOG and infrared reflections (ISCAN) simultaneously recorded eye movements. Subjects executed saccades to a mark 15° at right or left on a screen and back to fixation point/midline. 2 min EEG was obtained from each subject for each of the four possible saccades; rightwards R and leftwards L, towards (centripetal CP) and away from the midline (centrifugal CF) saccades. Each 500 ms window bracketing a saccade was analyzed using continuous wavelet transform (cWT). Single trial results were averaged after WT to obtain average gamma and also beta power values/coefficients for the perisaccadic time window. *T*-test was used to test for differences b/w PD and healthy subjects for frontal and parieto–occipital sites for both gamma and beta frequency ranges.

Results: (1) Average frontal PG power for healthy subjects; (CPR = 0.275, CFR = 0.27, CPL = 0.295, CFL = .285) vs. PD patients (CPR = 0.24, CFR = 0.22, CPL = 0.235, CFL = 0.235)_p = 0.0005.

(2) Average parieto–occipital PG power for healthy subjects; (CPR = 0.235, CFR = 0.23, CPL = 0.23, CFL = 0.23) vs. PD patients (CPR = 0.28, CFR = 0.27, CPL = 0.28, CFL = 0.29)_p = 0.0006.

(3) Average frontal PB power for healthy subjects; (CPR = 0.3, CFR = 0.29, CPL = 0.32, CFL = 0.31) vs. PD patients (CPR = 0.285, CFR = 0.275, CPL = 0.28, CFL = 0.29)_p = 0.03.

(4) Average parieto–occipital PB power for healthy subjects; (CPR = 0.26, CFR = 0.27, CPL = 0.27, CFL = 0.27)) vs. PD patients (CPR = 0.31, CFR = 0.31, CPL = 0.31, CFL = 0.32)_p < 0.0001.

(5) 'Frontal' PG and PB powers (coefficients) attenuate while both the 'parieto–occipital' PG and PB power increase in PD patients vs. age matched healthy subjects for all kinds of voluntary saccades. This happens for all kinds of saccades. Healthy subjects = CPR (R^2 = 0.9), CFR (R^2 = 0.8), CPL (R^2 = 0.9), CFL (R^2 = 0.9) and PD patients = CPR (R^2 = 0.3), CFR (R^2 = 0.2), CPL (R^2 = 0.2), CFL (R^2 = 0.3).

Discussion: Several brain areas are involved in cortical control of voluntary saccades. BOLD MRI shows (Rieger et al. 2008) that the frontal eye field (FEF) is hypoactive in PD patients during execution of voluntary saccades. Our results i.e. lower 'frontal' PG and PB power in PD vs. healthy subjects suggest an association between the EEG (Bodis-Wollner, 2002; Forgacs et al., 2008; Javaid et al., 2010) and BOLD-MRI (hypoactive FEF) results in PD.

Conclusion: Cortical saccade control is impaired in PD. The perisaccadic EEG reveals 'significantly' lower frontal and higher parieto–occipital PG and PB powers in Parkinson patients vs. healthy subjects. PG and PB power co-vary when voluntary saccades are executed except at frontal recording sites in PD. Since BOLD reveals reduced perisaccadic frontal activity, our current EEG results suggest a potential link between BOLD and EEG data.

doi:10.1016/j.clinph.2012.08.031

4. Anticonvulsant doses of 5-alpha-dihydroprogesterone and allopregnanolone: Behavioral toxicity results in male and female rats—Melanie Jeffrey (University of Toronto, Ont., Canada)

The effects of the hormones on seizures have been recognized for decades. One third of all women with epilepsy experience catamenial seizure exacerbation, an increased risk of seizures when plasma progesterone levels are low, or the ratio of estradiol to progesterone is high.

A primary metabolite of progesterone, 5-alpha-dihydroprogesterone (5αDHP), has recently been discovered by our laboratory to be the first compound to suppress the complex partial seizure focus in rats at non-toxic doses in over 25 years.

$$\text{Progesterone} \xrightarrow{5\alpha\ \text{Reductase}} 5\alpha\text{DHP} \overset{3\alpha\text{HSO}}{\longleftrightarrow} \text{Allopregnanolone}$$

Progesterone and allopregnanolone both confer seizure protection by activating $GABA_A$ channels, which accounts for their highly sedative side effects. A different and novel mechanism of anti-convulsant action, however, is implicated for 5αDHP; it is the only compound that suppresses the seizure focus in the amygdala-kindling model, has a rapid (15 min) onset of action, and subjects exhibit no ataxia or sedation. The discovery of 5αDHP's ability to control complex seizures at *non-sedating doses* deserves further research.

Behavioural studies of male and female rats have tested toxicity of anti-convulsant doses of 5αDHP and allopregnanolone. Compounds were administered intraperitoneally (ip) at doses that had produced anticonvulsant effects in earlier studies. The presenter will present results of the following behavioural experiments: The Elevated Plus Maze, a model of anxiety; the Morris Water Maze, a model of learning and memory; the Forced Swim Test, a model of depression; the Open Field Test, a model of locomotor and anxiety behaviours. Possible mechanisms of 5αDHP's anti-convulsant action will be explored in relation to current publications. Unexpected results and potentially confounding factors will be discussed.

Future electrophysiological and biomolecular experiments will produce data to elucidate the compound's novel mechanism of action. It is hoped that a better understanding of neurosteroids in epilepsy will lead to a better understanding of the pathophysiology of seizures, and improve treatment outcome.

doi:10.1016/j.clinph.2012.08.032

5. Why study event-related potentials in Rett Syndrome?—James Wark (CooperHealth, NJ, USA)

Event-related Potentials (ERP) are obtained from scalp EEG's recorded during the first 0.5 s after an event. Evoked Potentials are much earlier: for Auditory Potentials, the first millisecond after a click, reflecting activity in the brainstem. ERP, however, are influenced by cortical activity and are of great interest in conditions with cognitive impairment, like autism. Characteristic ERP abnormalities have been described in autistic Spectrum Disorders (ASD). Rett Syndrome (RS) has many symptoms in common with ASD. Furthermore, being due to a known genetic mutation, RS has a mouse model. ERP abnormalities have been described in mice. ERP from Rett Syndrome patients are somewhat ambiguous, especially in the light of studies of the animal model. ERP have been looked at with MEG in ASD; our study would study both scalp EEG and MEG.

doi:10.1016/j.clinph.2012.08.033

[1] Tel.: +1 718 270 7371.

6. Different strokes for different folks: The Toronto Chinese-Canadian stroke epidemiology study – 1990–2010—Joseph Y. Chu [a], Jason K. Chu [b], Derek K. Chu [c], Jack V. Tu [d] ([a] University of Toronto, Canada, [b] Emory University School of Medicine, USA, [c] McMaster University School of Medicine and Post-Graduate Studies, Canada, [d] Institute of Clinical Evaluative Sciences, University of Toronto, Canada)

Introduction: It has been recognized in the past few decades that different ethnic groups living in Canada may have different stroke patterns and epidemiology.

Methods: Two retrospective case-controlled studies were carried out between 1990 and 2000 to study the stroke characteristics and epidemiology of Chinese-Canadians living in Toronto. Statistical analysis was carried out by the Institute of Clinical Evaluative Sciences. A further smaller scale study was also carried out in the late 2000 to look at the relationship between stroke and diabetes mellitus amongst this population.

Results: Chinese-Canadians were found to have 1/6 the prevalence of extracranial vascular stenosis. They have a higher frequency of intracranial vascular disease which may be due to the higher frequency of hypertension and diabetes mellitus. Higher incidence of intracranial hemorrhage was found compared to Caucasian controls which may be due to the lack of awareness and optimal treatment of their hypertension.

Details of the results of these studies including statistical and clinical data will be presented.

Conclusions: This is the first long term retrospective study of the stroke patterns and epidemiology for Chinese-Canadians residing in Toronto. Further prospective population-based study will be essential to study the important interactions between genetics and environment in the pathogenesis of different strokes for different folks.

doi:10.1016/j.clinph.2012.08.034

7. Gamma knife treatment for symptomatic epilepsy due to vascular malformations—Emilie Lareau-Trudel [a], François Moreau [a], David Mathieu [b], Julie Duval [a], Charles Deacon [a] ([a] Service de Neurologie, Université de Sherbrooke, Sherbrooke, Que., Canada, [b] Service de Neurochirurgie, Université de Sherbrooke, Sherbrooke, Que., Canada)

Introduction: Detailed prospective studies are scarce on gamma knife treatment for arteriovenous malformations (AVM) or cavernous angioma (CA) regarding epilepsy outcome. The objective of this study is to further investigate prospectively the effect of gamma knife on seizures and expand our knowledge to other aspects of epilepsy management: medication, cognition and quality of life.

Method: We included prospectively 9 consecutive patients (4 AVM and 5 CA) who underwent radiosurgery for epilepsy caused by vascular malformation at the CHUS between August 2004 and August 2009. The mean marginal radiation dose was 20 Gy. The objective of this study is to determinate the seizure outcome after radiosurgery. Patients were followed every 3 months to evaluate seizure count over time, Engel score and medication status. Quality of life (QOLIE 89) and neuropsychological evaluation were completed before the treatment and at 12 and 24 months following the intervention.

Results: Patients were followed for a mean period of 39 months (range from 15 to 72 months). Three patients have been seizure free for 1 year (33%). Overall 5 patients (55%) had significant improvement with an Engel score of 1 (completely seizure free or non disabling simple partial seizure only). Medication status did not change over time. The QOLIE 89 score improved by more than 25 points (on a 100 points scale) in 3 patients (43%), 2 patients (29%) reported no change and 2 patients had lower scores. Neuropsychological testing did not show any deterioration in cognition following the intervention. No adverse reaction occurred so far.

Conclusion: Stereotactic radiosurgery has some efficacy for the treatment of epilepsy associated with vascular malformations and improves quality of life in a majority of patients. It seems less effective than surgical lesionectomy. No cognitive or physical morbidity was observed. This treatment could be a useful alternative for vascular lesions in eloquent areas that cannot be safely removed with microsurgery.

doi:10.1016/j.clinph.2012.08.035

8. Angelman Syndrome revisited: An update in 2011—Lolita Niedermeyer, James Wark, Joseph Chu, Paul A. Hwang (Mohawk-McMaster IAHS, CooperHealth NJ, William Osler Health Centre, North York General Hospital, University of Toronto Epilepsy Research Program, Toronto, Ont., Canada)

Aim: Retrospective analysis of the clinical features, EEG and chromosomal findings in Angelman Syndrome (AS), a congenital developmental disorder due to del15 q 11–13.

Methods: A 20 year old man was diagnosed at age 4 years, with global developmental delay, seizure disorder with status epilepticus and R. hemiparesis, on AEDs.

Results: The diagnosis of AS was confirmed by chromosomal analysis: deletion of the maternal 15 q 11–13. The clinical phenotype comprises infantile spasms with hypsarrhythmia on the EEG, secondary generalized seizures intractable to AEDs, leading to status epilepticus, postictal hemiparesis; global developmental delay without speech development and autistic-type behaviour. Current medications: Depakote sprinkles©, lamotrigine and carnitine.

The EEG was invariably abnormal: modified hypsarrhythmia in infancy (West syndrome), diffusely slow background activity, central spikes (at times synchronized with hand clapping) and multifocal epileptiform features, slowly progressive to low-amplitude attenuation of background, suggestive of an epileptic encephalopathy with multiple independent spike foci.

Discussion: The presence of epileptiform activity is likely due to mutations at subunits of the GABA-A receptor genes in the deleted segment on the long arm of maternal chromosome 15q 11–13, reducing the expression of ubiquitin ligase 3A (UBE3A) gene. Paradoxically, the same deletion of the paternal chromosome 15 produces the phenotype of the Prader–Willi Syndrome (PWS): hyperphagia, obesity and hypomentia, rare seizure activity and usually a normal EEG. The underlying basis of this genetic imprinting is not completely understood.

Conclusion: These "experiments of Nature" with AS and PWS reveal the complexity of the genetic bases of some of the epilepsy syndromes of childhood.

doi:10.1016/j.clinph.2012.08.036

9. Network density and synaptic weight mechanisms for non-evoked transitions in cognition and EEG—Elan Liss Ohayon [a,b,c], Ann Lam [c], Ursula Bellugi [c], Terry J. Sejnowski [a,b] ([a] Computational Neurobiology Laboratory, The Salk Institute, La Jolla, CA, USA, [b] The Institute for Neural Computation, University of California, San Diego, CA, USA, [c] Laboratory for Cognitive Neuroscience, The Salk Institute, La Jolla, CA, USA)

A major challenge in neuroscience is to understand how neural systems respond to external stimuli. An often ignored but even

greater challenge is to understand how neural systems make decisions independently of external input. In this presentation we will show how two complementary mechanisms can support and modulate autonomous transitions in complex persistent activity: (1) network density and (2) synaptic weights. Computational models with random, ring and spatial connectivity are applied to help illustrate how changes in synaptic weights can effect changes to frequencies and the occurrence of frequency sweeps observed in EEG recordings. Simulations iterating across excitatory and inhibitory weight combinations (E → E; E → I; I → E; I → I) show that changes in all types of connections can have non-linear effects on activity propagation properties. For example, changing excitatory → excitatory connections in a network with fixed density can result in large shifts in activity frequency. Peak population frequencies range from approximately 20 Hz to 80 Hz with a tendency to rise as the E → E weighting is increased. These changes in spectral properties tend to be even more complex and non-monotonic in response to changes in connections to and from inhibitory populations. In turn, changes to the cellular density of two- and three-dimensional networks alter the spatial and spectral nature of activity propagation allowing for complex formations such as spiral waves and the emergence of autonomous transitions. Together, the co-modulation of weight and density parameters allows for complex, persistent activity with a range of frequency distributions and autonomous transitions patterns. The effects of the interactions of these two mechanisms suggest that alterations to network density along with weight modulations may be key factors in enabling EEG transitions that can occur independently of external input. The two mechanisms may thus be important evolutionary, developmental, and learning strategies for dynamical tuning of neural population activity underlying cognition.

Support contributed by: CIHR, NIH.

doi:10.1016/j.clinph.2012.08.037