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1 The anticonvulsant effects of progestoerone and 5α-dihydroprogesterone on amygdala-kindled seizures in rats – W. McIntyre Burnham, Deborah Lonsdale (Department of Pharmacology, Bloorview Epilepsy Research Program and the University of Toronto, Toronto, ON, Canada)

Purpose: Progesterone is a recognized anticonvulsant in several animal seizure models. The purpose of this study was to investigate the anticonvulsant action of progesterone and its primary metabolite 5α-dihydroprogesterone (5α-DHP) in the amygdala kindling model.

Methods: Female Wistar rats were implanted in the right basolateral amygdala with a bipolar electrode. The subjects were kindled to 30 stage 5 seizures and stability tested. Multiple doses of progesterone and 5α-DHP were then tested for anticonvulsant activity against focal and generalized kindled seizures. The time course of progesterone's anticonvulsant action was also examined.

Results: Progesterone had an ED_{50} of 103 mg/kg against generalized convulsions at 15 min post-injection. Subjects were not sedated at the time of seizure testing, although sedation developed later. In time-course experiments, it was found that progesterone caused complete suppression of the generalized convulsion from 20 to 160 min post-injection. Suppression of the focal discharge was seen in some animals between 20 and 160 min. 5-α-DHP had an ED_{50} of 2.9 mg/kg against generalized convulsions and an ED_{50} of 4.3 mg/kg against focal seizures at 15 min post-injection. 5α-DHP did not produce sedation at any time interval.

Conclusions: Progesterone is a weak anticonvulsant when tested against amygdala-kindled seizures. 5α-DHP is a strong non-sedative anticonvulsant, effective against both the focal seizure and the generalized convulsion.

2 Propagation of amygdala-kindled seizures to the hippocampus in the rat: EEG features and behavioral correlates – D.S. Hewapathirane, W.M. Burnham (Epilepsy Research Program and Department of Pharmacology, University of Toronto, Toronto, ON, Canada)

Background: Kindling is an experimental animal model of temporal lobe epilepsy. The repeated application of sub-convulsive electrical stimulation to a discrete brain structure results in the progressive development of focal seizures, and the eventual appearance of fully generalized convulsions. Amygdala kindling has been pharmacologically validated as a model for complex partial seizures of temporal lobe origin, with secondary generalization. It is not clear which, and in what order, brain structures are recruited (into seizure activity) during the progression of the kindling phenomenon. The purpose of the present experiment was to investigate the propagation of amygdala-kindled seizures to the dorsal and ventral hippocampus.

Methods: Adult, male, Sprague-Dawley rats served as subjects. Three chronically indwelling, bipolar depth electrodes were surgically implanted in (i) the basolateral nucleus of the right amygdala (stimulating and recording); (ii) right/ipsilateral (with respect to site of stimulation) hippocampus (recording); and left/contralateral hippocampus (recording). Hippocampal electrodes were bilaterally implanted at either the dorsal ($n = 6$) or ventral ($n = 8$) level. Kindling stimulation was delivered twice daily for 5 days per week until the appearance of 10 fully generalized (stage 5) seizures, in all subjects. During each session, EEG recording and behavioral seizure scoring was performed.

Results: Afterdischarges were recorded in the amygdala at the outset of kindling, in all subjects. Delay to recruitment (into seizure activity) for the various extra-focal recording sites were as follows (mean number ± SEM of amygdala afterdischarges elicited): (i) ipsilateral ventral hippocampus (4.0 ± 0.9); (ii) ipsilateral dorsal hippocampus (6.2 ± 1.4); (iii) contralateral dorsal hippocampus (7.5 ± 1.4); (iv) contralateral ventral hippocampus (8.5 ± 1.0). The state of seizure progression (i.e. severity relating to level of seizure generalization) at the time of ipsilateral hippocampal recruitment was between stages 1 and 2 (partial seizures); whereas for the contralateral hippocampus, recruitment to seizure activity was between stages 2 and 3 (transition to generalized seizures). There was a statistically significant ($P < 0.05$) delay in the propagation of seizure activity (from the amygdala) to the contralateral hippocampus, compared to the ipsilateral hippocampus. Although a similar difference was evident in the delay to propagation to the dorsal hippocampus compared to ventral hippocampus, this was not statistically significant. Secondary and 'tertiary' afterdischarges were observed in most subjects, although not consistently. The first occurrence of secondary afterdischarge never preceded the recruitment of the contralateral hippocampus into seizure activity. The contralateral hippocampal afterdischarge was almost always time-locked with generalized convulsive behavior. In some instances, the amygdala and hippocampal afterdischarges were transiently asynchronous.

Conclusions: The results of the present study demonstrate that when kindling from the amygdala, the hippocampus will not be recruited into seizure activity immediately. It is clearly evident that the hippocampus will sustain fewer afterdischarges compared to the site of stimulation, during amygdala kindling. The observation that the left and right hippocampi are not recruited into seizure activity simultaneously is also noteworthy. It appears that the ipsilateral hippocampus becomes involved during partial seizure activity, whereas the contralateral hippocampus only begins to discharge at the time seizure generalization is first seen. This close link between contralateral hippocampal involvement and seizure generalization warrants further study, and may lead to a better understanding of the pathways involved in seizure spread.

3 Comparison of Close Return and Fourier detection of unstable periodic events in interictal and ictal EEG – H.Y. Chun[a], E. L. Ohayon[c], H.C. Kwan[b], W.M. Burnham[a,c], P.A. Hwang[c] ([a]Department of Pharmacology, [b]Department of Physiology and [c]Epilepsy Research Program, Institute of Medical Science, University of Toronto, Toronto, ON, Canada)

Close Return is a mathematical algorithm able to identify unstable periodic orbits in waveform signals. In this study we compare Close Return to Fourier analysis and consider the limitations of both techniques when applied to various EEG signals. Test data were collected from 12 randomly selected cases of localization-related epilepsy out of a database of about 1500 cases who had partial seizures recorded on digital 24 channel EEG, including inter-ictal, pre-ictal, ictal and post-ictal epochs. The comparison of close return to Fourier analysis of modeled data and the EEG data illustrates the ability of Close Return to identify and categorize unstable orbits of different periods. In contrast, these examples illustrate the

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limitation of Fourier with respect to identifying unstable periodic orbits as well as events of undetermined duration. We highlight the fact that if Close Returns are considered to be markers of instability, a false positive determination will be made if presented with highly periodic data. This observation suggests that a combination of traditional Fourier analysis and Close Returns may offer a promising way of differentiating and quantifying the degree to which an unstable periodic signal is approaching periodicity. The application of Close Return in conjunction with Fourier-based methods to the analysis of EEG signals may be particularly helpful for on-line detection and categorization of ictal and non-ictal events.

4 Families with epilepsy: a genetic study in progress – Paul A. Hwang, Lia Stenyk, Julie Mak, Berge Minassian (Department of Paediatrics, North York General Hospital, Toronto, ON, Canada; Brock University, St. Catherines, ON, Canada; Hospital for Sick Children, University of California, San Francisco, CA, USA; Epilepsy Research Program, University of Toronto, Toronto, ON, Canada)

Rationale: A number of epileptic disorders have been linked to single-gene mutations encountered in large families, but there is no population-based study of genetic epilepsies, carefully defined by clinical semiology, EEG analysis and pedigree analysis.

Methods: The current study defines epileptic syndromes in well-characterized families involving two or more generations, affecting 3 or more individuals, followed prospectively by neurologists with a special interest in genetic epilepsy, with access to 20 years of EEGs from early infancy to adulthood. The information and consents were obtained following ethical guidelines of the Canadian Tri-Council recommendations and approved by the IRB of the HSC.

Results: To date, 56 families have agreed to have their pedigrees entered into a secure common database, covering two or more generations, involving at least 3 first-degree relatives. These are likely genetically informative for a single mendelian genetic defect linked to their epilepsy. Careful analysis of their EEG studies is in progress, following ILAE classification of the epilepsies.

Conclusion: This study analyzes families with epilepsy and aims to select out genetic disorders linked to a single mendelian gene, as a first step towards isolating gene defects underlying specific epileptic syndromes.

5 Symptomatic infantile spasms demonstrate heterogeneous anticonvulsant responses following treatment with ACTH and vigabatrin – Morris H. Scantlebury, Duy Tran, George Karvelas, Lionel Carmant (Department of Neurology, Hôpital Ste-Justine, Montréal, QC, Canada)

Introduction: Infantile spasms are an age-related epileptic disorder occurring in children most commonly before the first year of life. When associated with hypsarrhythmia and developmental regression (West syndrome) the outcome may be catastrophic, with 80% of children progressing to develop mental retardation along with chronic epilepsy.

Rationale: In infantile spasms it is well recognized that adequate seizure control can improve outcome. Both ACTH and vigabatrin have been shown to be effective treatments for the seizures; however, debate remains as to which should be used as first-line therapy. The goal of this study was to compare their effectiveness in the resolution of infantile spasms as broadly classified into symptomatic, cryptogenic and idiopathic groups.

Methods: We have reviewed 70 cases of infantile spasms treated at our institution between the years 1990–2000, which we divided into three groups: symptomatic $n = 38$ (54.3%), cryptogenic $n = 18$ (25.7%), and idiopathic $n = 14$ (20%).

Results: Hypsarrhythmia was found on the EEG in 12/14 (85.7%) of the idiopathic group. This group also responded best to treatment with seizure freedom obtained in 6/7 (85.7%) of children treated with ACTH and 7/8 (87.5%) treated with vigabatrin. In the symptomatic group, non-responders to ACTH, 11/16 (68.8%) were significantly higher than those for vigabatrin 6/22 (27.3%), $P < 0.05$. There were no other significant differences noted between the groups.

Conclusion: We report a higher prevalence of idiopathic infantile spasms in our study population than that reported in more recent series. We conclude that vigabatrin is as effective as ACTH for the treatment of the cryptogenic and idiopathic groups, and that symptomatic infantile spasms respond better to treatment with vigabatrin than to ACTH.

6 Time course of occipital gamma range EEG during voluntary saccades in the dark – Peter B Forgacs[a,c], Nasir Syed[a], Hans von Gizyczki[b], Mat Avitable[b], Ivan Bodis-Wollner[a] ([a]Department of Neurology and [b]Scientific Computing Center, SUNY Downstate Medical Center, New York, NY; [c]Department of Neurology, University of Szeged, Szeged, Hungary)

Purpose: To investigate if EEG gamma power laterality correlates with the saccade direction.

Rationale: Occipital gamma coincides with visual stimulation. By studying saccades in the dark we avoided the 'confounding' effects of visual stimulation.

Methods: Twelve volunteers (age 19–64 years) were studied. Saccades were executed between two memory positions 35° apart at a distance of 78 cm from the eye. Twelve channels of EEG were recorded over occipital and parietal locations. Eye movements were recorded with EOG and infrared corneal reflection scanning (ISCAN). Perisaccadic EEG was divided into 4 time windows, 150 ms windows before, 75–75 ms during and 150 ms after the saccade. Wavelet coefficients were quantified using continuous wavelet transform followed by Hilbert transform on gamma (37.24 Hz). Statistics: Mixed general linear model, analysis of variance (ANOVA). Factors: saccade direction, time window and channel. Contrasts within ANOVA were determined for 5 homologous channels depending on saccade direction. An interaction between saccade direction and gamma power for each electrode pair was assessed in all time windows.

Results: There was a significant interaction between saccade direction and gamma power at the lateral occipital electrodes in the intrasaccadic period. Gamma power is higher ipsilaterally to the direction of the saccade.

Conclusion: Intrasaccadic occipital gamma appears in the absence of visual input, consistent with preparatory activity for new fixation. The significance of ipsilateral dominance needs further investigation.

7 Epileptiform abnormalities in children with language regression – Kathryn McVicar, Shlomo Shinnar, Karen Ballaban-Gil, Roberto Tuchman, Isabelle Rapin, Solomon Moshe (Albert Einstein College of Medicine and Montefiore Medical Centre, Bronx, NY)

Background: Language regression, or loss of previously acquired language, occurs in children in several settings. The most common is in the context of a more global autistic regression, typically seen prior to age 3 years [1-3]. It can also occur in isolation or as part of the Landau-Kleffner (acquired epileptic aphasia) or ESES (electrographic status epilepticus in sleep) syndromes. Whether the EEG abnormalities are a fundamental part of the pathophysiology or an epiphenomenona remains controversial [4-6].

Methods: Findings from all-night video EEG monitoring of 122 children with language regression who underwent video EEG monitoring at the Comprehensive Epilepsy Center Epilepsy Monitoring Unit at the Montefiore Medical Center between 1991 and 2002, with a single patient from 2003, are reported. All children had documented language regression (loss of at least 5 previously acquired words) with or without associated autistic regression.

Results: Of the 122 children, 74 (61%) had normal video EEG monitoring while 48 (39%) had abnormal EEG findings. The later group includes 39 (32%) with epileptiform abnormalities and 9 (7%) with purely nonepileptiform abnormalities. Epileptiform abnormalities included 17/48 (35%) with bilateral, 17/48 (35%) with left, 8/48 (17%) with right and 6/48 (13%) with generalized or multifocal discharges. ESES pattern was present in 11/48 (23%). Epilepsy was present in 11 (10%). Nonepileptiform abnormalities occurring without epileptiform activity included generalized background slowing in 6/9, disorganization in 2/9 and right temporal intermittent polymorphic slowing in 2/9 children.

Conclusion: Children with language regression are more likely to have epileptiform records than to have epilepsy. Left-sided and bilateral findings occurred more frequently than right-sided, generalized or multifocal findings. Whether or not these epileptiform abnormalities are all part of the Landau-Kleffner spectrum or not is unclear as some of the children with epileptiform EEGs clearly had a more global autistic regression. The relationship between epileptiform EEG abnormalities and underlying pathophysiology of language regression requires further investigation.

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8 Computer reading of the human EEG – Robert Cohn[a], Russell L. Myers[b], Stephen D. Ousley[c] ([a]Howard University Hospital, Washington, DC, USA; [b]Long Island University, Southampton Campus, Long Island, NY, USA; [c]Smithsonian Institution, Washington, DC, USA)

This represents 122 subjects of a total of over 600 patients with normal and abnormal EEGs routinely recorded during the past several years. These were all 8 channel records with electrodes placed over homologous regions of the head. One hundred and twenty seconds of EEG data were obtained from each individual. Three different major frequency/duration measurements were utilized. One was the mean frequency, the second, the percent of slow waves greater than 18% in any lead, and the third was the confidence kernel of 'chaos' scatter plots in any channel. The confidence kernel is an index of dispersion of EEG data. Strict concordance was obtained between the clinically read EEG record in 91% using the mean frequency values, 91% using the slow waves, and 93% using the confidence kernel areas. When minimal differences in measurement were utilized from the discordant data, the useful concordance ranged above 95%. These data suggest that the stability, and objectivity of such computerized observations would be a healthy adjunct for routine clinical EEG work.

9 Restless leg syndrome exacerbating adult absence seizures – A.J. Rodriguez, M. Sammaritano, B.L. Ehrenberg (Tufts-New England Medical Center, Boston, MA, USA)

Objective: To report a series of patients in which the appearance of restless legs syndrome coincided with the reappearance of absence seizures.

Background: Poor sleep exacerbates seizures. Obstructive sleep apnea (OSA) has been described to worsen seizure control and its treatment has been shown to improve seizures. Periodic leg movement of sleep (PLMS) and restless leg syndrome (RLS) have not been studied regarding seizure control. Improving sleep and treatment of these sleep disorders can benefit epilepsy patients' treatment.

Design/Methods: Series of cases followed independently over the years by the authors. Clinical history, physical examination, polysomnography (PSG) and electroencephalogram (EEG) results and treatment outcome are described.

Results: (1) An 18-year-old right-handed woman presented with seizures consisting of staring episodes, slight head nod and eyelid fluttering lasting 4–6 s. Physical examination and magnetic resonance imaging (MRI) were normal. EEG showed generalized 4–6 Hz spike-wave activity. Her PSG showed 77 unexplained arousals with spontaneous PLMS. She had a total arousal index (TAI) of 18/h. She had a history of absence seizures since she was 6 years old and remained seizure-free for at least 5 years. Months before, she had been complaining of excessive daytime sleepiness (EDS), increased leg movements at night and restlessness of legs in the daytime. Her seizures were difficult to control until she was placed on carbidopa/levodopa and later on pramipexole. (2) A 32-year-old right-handed man presented with staring episodes lasting 20–30 s with a frequency of 1–2 a day. His physical examination and brain MRI were normal. One year before he noticed increased fatigue, daytime sleepiness and leg movements during sleep. EEG showed spike-wave complexes, generalized maximum bilateral frontal. PSG demonstrated PLMS [periodic limb movement index (PLMI) of 10.9/h], 60% of them associated with arousals. TAI was 15.6/h. He had a history of absence seizures starting at age 4 years. He was seizure-free for 20 years before this recurrence. Valproic acid achieved some control of the events and the seizures disappeared completely with the addition of carbidopa/levodopa and later pramipexole. (3) An 18-year-old right-handed man presented with the first episode of generalized tonic-clonic seizures. He also had episodes of unresponsiveness lasting 2–3 min. EEG showed bursts of generalized spike-wave activity during these episodes. His physical examination was normal. He had a 16 year-old brother with absence since childhood. He noticed EDS and fatigue months before the seizures. His PSG showed PLMS (PLMI of 3.3/h). He was treated with topiramate and gabapentin with improvement of his seizures and PLMS. (4) A 41-year-old woman had staring episodes and unresponsiveness with occasional GTC seizures. Her EEG showed bursts of high voltage 3.5–4 Hz generalized spike-wave and polyspike-wave activity lasting 2–3 s without clinical correlations. Her PSG showed a PLMI of 21.4/h, associated with arousals. TAI was 13.1/h.

Conclusions: Sleep disorders other than sleep apnea can worsen seizure control in epilepsy patients. Furthermore, the relationship of restless leg syndrome and/or periodic limb movements of sleep and the reappearance of absence seizures requires further investigation. We should remember that the leg movements tend to be genetically linked, as do some types of seizures, but they may not become prominent until later in life.

10 The epileptic pre-aura – E. Niedermeyer (John Hopkins University, Baltimore, MD, USA)

Epileptic seizures of focal/regional origin are quite often preceded by an aura which is a subjective ictal experience, usually associated with ictal EEG firing but unassociated with objective/behavioral changes. The duration of an aura varies from seconds to about 1 min. There is now good evidence that an aura can be preceded by a pre-aura lasting 1–10, perhaps even 20, min. The scalp EEG of a pre-aura is unremarkable but some changes have been found in various methods of quantified EEG (while the patient is unaware of any ictal change). Vascular changes have been demonstrated during the pre-aura: especially hyperemia over large neighboring areas whereas ischemic microcirculation is noted in the immediate neighborhood of the focus (presumably due to acute ictal astrocytic swelling obstructing capillary flow). The study of ultrafast EEG frequencies (80–1000 Hz) might shed more light on the pre-aura (presumably showing electro-decremental changes). The occurrence of vascular changes in the pre-aural state is no basis for the theory that 'epilepsy is a primarily vascular disorder.' Neuronal initiation appears to be a fact.