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1. Prolonged hyperthermic seizures in rats with focal cortical dysplasia lead to hemispheric and hippocampal asymmetry—Steve A. Gibbs, Morris H. Scantlebury, Pablo Lema, Joseph B. Essouma, Lionel Carmant (CHU Ste-Justine Research Center, Ste-Justine Hospital, Université de Montréal, Montréal, Canada)

Rationale: Atypical febrile seizures have been associated, in retrospective studies, with the mesial temporal lobe epilepsy. Recently, we have demonstrated that a cortical microgyrus predisposes immature rats to prolonged hyperthermic seizures (HS) and chronic epilepsy. The purpose of this study is to investigate the effects of prolonged HS on brain development and to assess the impact of seizure duration.

Methods: Freeze lesions (focal microgyri) were induced in the right fronto-parietal cortex of rats on postnatal day (P)1. HS were then induced at P10 by exposure to moderately-heated dry air. To evaluate hippocampal and extrahippocampal asymmetry, right and left hemispheric, cortical, subcortical and hippocampal volumes were estimated at P22. The degree of asymmetry was estimated by calculating a ratio between the volumes of the right and left structures. To assess the role of seizure duration, we prevented the prolonged HS by administering diazepam to a subgroup of rats.

Results: Hemispheric asymmetry ipsilateral to the lesion was observed in lesioned rats with HS. When their hemispheres were divided into cortical and subcortical volumes, asymmetry was only seen in the cortex. However, when the hippocampal volume was assessed independently, hippocampal asymmetry was observed. Of these rats, 29% (5/17) had severe hippocampal atrophy. Decreasing the duration of the HS did not significantly reduce the overall hemispheric asymmetry or the cortical asymmetry. However, hippocampal asymmetry was not observed in lesioned rats with shorthened HS. No hippocampal or extrahippocampal asymmetries were seen in any other control groups.

Conclusion: Our findings support a link between the prolonged febrile seizure and volume abnormalities in the predisposed brain. More importantly, we demonstrate that early seizure termination can prevent hippocampal volume changes. Ongoing studies are looking at the underlying pathophysiological mechanisms.

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2. The anticonvulsant effects of progesterone and its metabolites on amygdala kindled seizures in male rats—Deborah Lonsdale, Kirk Nylen, W. McIntyre Burnham (University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontanrio, Canada)

Purpose: Progesterone is a neurosteroid that modulates neuronal excitability. The anticonvulsant effects of progesterone are largely mediated by the actions of its metabolites. The mechanism of the antiseizure action of progesterone is an important consideration in the development of anticonvulsant drugs with novel mechanisms of action. New drugs are needed for the treatment of seizures that are currently drug resistant. The purpose of this study was to measure the anticonvulsant effects of progesterone, 5alpha-dihydroprogesterone, and allopregnanolone against amygdala-kindled seizures in male rats. The amygdala kindling model is a model of human complex partial seizures with secondary generalization. Complex partial seizures are often drug resistant.

Methods: A bipolar electrode was chronically implanted in the right amygdala of male Wistar rats. All subjects were kindled to 30 stage 5 seizures and stability tested. Multiple doses of progesterone, 5alpha-dihydroprogesterone, or allopregnanolone were administered in separate dose-response studies. The antiseizure effects of each compound were determined against both the focal electrographic and the generalized convulsive seizure. A progesterone time-response study was also conducted.

Results: At 30 min after injection, progesterone had an ED_{50} of 65.3 mg/kg against generalized convulsions and an ED_{50} of 114 mg/kg against the focal seizure. Ataxia was observed in some subjects when large doses ($\geq$80 mg/kg) were administered. In the progesterone time-course study, it was found that 160 mg/kg of progesterone completely suppressed the generalized convulsion from 40 to 80 min following injection. During this period, suppression of the focal discharge was also seen in some of the subjects. 5alpha-dihydroprogesterone had an ED_{50}

of 6.2 mg/kg against both the generalized seizure and the focal seizure. Allopregnanolone had an ED_{50} of 15.2 mg/kg against the generalized seizure and was not effective against the focal seizure.

Discussion: Progesterone is an effective anticonvulsant against the generalized convulsive component of amygdala-kindled seizures in male rats. Progesterone is only effective against the focal seizure at high ataxic doses. 5alpha-dihydroprogesterone is a potent anticonvulsant against both the kindled amygdala focal discharge and the generalized convulsion. Allopregnanolone is an effective anticonvulsant against the generalized convulsion, but not against the amygdala focal discharge.

3. A ketogenic diet and diallyl sulfide do not elevate afterdischarge thresholds in kindled rats—Kirk Nylen, Sergei Likhodii, Kathryn Hum, W.M. Burnham (University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada)

Introduction: Acetone has been implicated as a potential mechanism for the anticonvulsant actions of the ketogenic diet (KD). Rats fed a ketogenic diet, however, do not appear to develop high blood-acetone levels like humans do. Coincidentally, in our hands the KD has lacked anticonvulsant actions in rats. The purpose of the present study was to determine whether inhibition of acetone metabolism, in rats fed a ketogenic diet, corresponded to increases in afterdischarge thresholds in fully kindled subjects.

Methods: Twenty four adult male rats were kindled to 30 stage-5 seizures before afterdischarge thresholds (ADT) were determined. Subjects were placed in one of four groups (KD + diallyl sulfide (DAS); KD + vehicle; control diet (CD) + DAS; CD + vehicle) and stimulated every other day. Blood sampling and gavaging were also performed every other day, on non-kindling days. Blood was analyzed for glucose, beta-hydroxybutyrate, acetoacetate, and acetone content. After 20 days, ADTs were redetermined.

Results: Blood acetone concentrations were significantly higher in the KD + DAS group compared to other groups. None of the treatments, however, elevated ADTs.

Conclusions: The KD was unable to elevate ADTs in fully-kindled rats. Although subjects in the KDD group achieved significant elevations of blood acetone, these concentrations (i.e. $\sim$0.2 mM) are much lower than those ($>$2.0 mM) shown to confer anticonvulsant activity previously. There appears to be large variability between humans and rats in terms of their ability to produce elevated blood acetone levels. Overall, these data further agree with the hypothesis that acetone may play a role in the KD's anticonvulsant mechanism. These data also suggest that adult rats are not ideal subjects for modeling the anticonvulsant actions of the KD.

4. Kindled seizures enhance young neuron survival in the adult rat dentate gyrus—Brian Scott, W.M. Burnham (University of Toronto Epilepsy Research Program, University of Toronto, Toronto, Ontario, Canada)

New neurons continue to be generated throughout adulthood in the dentate gyrus of mammals. This process of neurogenesis is believed to play a role in some forms of learning and memory. Hippocampal-dependent learning tasks have been shown to specifically enhance the survival of new granule neurons. The present study examined the effects of kindled seizures in rats on the survival of young neurons born before the kindling began. Kindled seizures within the perforant path input to the dentate gyrus triggered between 1 and 2 weeks following the injection of bromodeoxyuridine (BrdU), were found to increase the number of BrdU and NeuN co-labeled cells in the granule cell layer by 128% 1 month later. The number of co-labeled cells was not correlated with measures of seizure severity. These results demonstrate that kindled seizures enhance the survival of new born neurons in the adult rat dentate gyrus which may reflect the actions of an activity-dependent mechanism normally involved in hippocampal-dependent learning and memory.

5. Particularities of the spontaneous and flash evoked EEG rhythms in children with febrile seizures—Birca A., Carmant L., Lortie A., Vannasing P., Lassonde M (Centre de Recherche, Hôpital Sainte-Justine, Université de Montréal)

A number of EEG abnormalities such as spike and wave discharges, sharp waves, diffuse slowing, focal theta rhythms and photoparoxysmal reactions have been described in children with febrile seizures (FSs).

The aim of this study was to compare the spontaneous and flash evoked EEG rhythms in children with FSs and normal controls. We used Fourrier transform and steady-state visual evoked potentials (SSVEPs) to quantify the spontaneous EEG spectrum and the magnitude of flash evoked responses, respectively. EEG was recorded in twenty 3–4 year-old children with FS and eight age-matched controls, as well as in 11 5–7 year-old children with FSs and 7 controls. Our data suggest that the 3–4 year-old children with FSs show greater magnitudes of the spontaneous EEG spectra (mainly theta band) compared to controls, whereas older children with FSs (5–7 year-old) show greater SSVEPs amplitudes compared to controls. These data suggest that the susceptibility for seizures could be assessed by different techniques on the EEG record of children with FSs depending on their developmental stage.

6. Triphasic waves versus nonconvulsive status epilepticus: EEG distinction—Martin Boulanger, Charles Deacon, Diane Lécuyer, Sylvie Gosselin, Jean Reiher (Department of Neurology, Centre Hospitalier Universitaire de Sherbrooke)

Background: Triphasic waves (TWs) and generalised non-convulsive status epilepticus (GNGSE) share morphological features that may create diagnostic ambiguity.

Objective: To describe electroencephalographic differences between TWs and GNCSE.

Methods: We retrospectively compared the EEGs of two groups of patients presenting with decreased level of consciousness; those with TWs associated with metabolic encephalopahty and those with GNCSE. We studied the following: demographics, etiology and EEG morphological features. All EEGs were classified blindly (TWs or GNSCE) by two expert EEGers. Agreement between experts and concordance with clinical diagnosis were measured.

Results: We analysed 87 EEGs (71 patients) with TWs and 27 EEGs (13 patients) with GNCSE. Agreement between experts and concordance with clinical diagnosis were excellent. When compared to TWs, epileptiform discharges associated with GNCSE had a higher frequency (mean = 2.4 vs. 1.8 Hz) ($P < 0.001$), a shorter duration of pahse one ($P = 0.001$), extra-spikes components (69 vs. 0%) ($P < 0.001$) and less generalised background slowing (15.1 vs. 91.1%) ($P < 0.001$). Amplitude predominance of phase two was common with TWs (40.8 vs. 0%) ($P = 0.01$). Lag of phase two was absent in all cases of GNCSE but present in 40.8% of patients with TWs. Noxious or auditory stimulation frequently increased the TWs (51%) while it had no effect on the epileptiform pattern ($P = 0.008$).

Conclusions: Certain EEG morphological criteria and the response to stimulation are very helpful to distinguish TWs from GNCSE.

7. The contribution of hippocampal developmental malformation to epileptogenicity: an intracranial SEEG study—Martin Holtkamp, Demet Kinay, Eliane Kobayashi, Neda Bernasconi, Frédérick Andermann, André Olivier, Andrea Bernasconi, Jean Gotman, François Dubeau (Montreal Neurological Institute and Hospital, McGill University)

Purpose: To assess epileptogenicity of hippocampal formations (HF) with developmental changes (Baulac et al., Ann Neurol 1998; 44:223) through SEEG.

Methods: Seventy three patients with focal epilepsy who underwent at least bilateral temporal lobe SEEG evaluation between 1995–2005 were studied, and divided in 3 groups based on MRI findings: group 1 ($n = 17$ patients) with malformed HFs ($n = 27$), group 2 ($n = 25$) with atrophic hippocampus ($n = 34$) and group 3 ($n = 31$) with normal hippocampi. To assess epileptogenicity of the malformed HF, we compared the interictal (IEA) and ictal epileptiform activity in limbic structures. We also analysed epileptogenicity of other temporal and extra-temporal ($n = 39$ patients) structures.

Results: In the limbic and extra-temporal neocortical structures, IEA was recorded equally in all groups. All patients with malformed HF (group 1) showed neocortical temporal IEA, but fewer in group 2 (76%, $P = 0.034$) and group 3 (58%, $P = 0.001$). Limbic seizure onsets were more frequent in malformed HF and atrophic hippocampi compared to normal hippocampi (63 and 82 vs. 37%, $P = 0.021$ and $P < 0.0001$). Regional temporal seizure onsets occurred more often in group 1 (65%) than group 3 (32%, $P = 0.031$) but not differently from group 2 (44%). Extra-temporal seizure onsets were equal in all groups. Temporal lobe resection only led to unfavourable outcome (Engel's class III–IV) in groups 1 (6/9 patients) and 3 (12/18) compared to group 2 (4/18, $P = 0.019$ and 0.009).

Conclusions: This study demonstrates that malformed HFs generate epileptic activity, but in association with widespread epileptogenicity as most patients show neocortical temporal or extra-temporal epileptic discharges and poor outcome after temporal lobe surgery only.

8. Gamma-hydroxy butyrate for acute hemiplegia of childhood: a prolonged EEG study—Paul A. Hwang[1], Brian Katchan[2] and Mortimer Mamelak[3] ([1]North York General Hospital and the University of Toronto Epilepsy Research Program, Toronto, Ontario, Canada, [2]Department of Medicine and Critical Care, North York General Hospital, Toronto, Ontario, Canada, [3]Baycrest Centre and University of Toronto, Toronto, Ontario, Canada)

Aim: To study EEG changes following acute gamma-hydroxy butyrate (GHB) therapy of acute hemiplegia of childhood (AHC).

Rationale: AHC is a disorder in young children characterised by acute hemiplegia of one or both sides, of unknown etiology, but probably due to energy deficiency in affected motor systems, and possibly related to hemiplegic migraines.

Previous studies have found no changes or only lateralised slow waves in the EEG. About 50% of children develop seizures, developmental delay, involuntary movements.

GHB, a precursor for GABA synthesis in the brain, also enters the Krebs cycle and produce more ATP, hence energy for affected regions. The efficacy of GHB in treating AHC and preventing some of the late sequelae is unknown.

Study design: An $N = 1$ study of a female infant, aged 18 months was undertaken. Normal at birth and early development she began with acute hemiplegic episodes in the first year of life, of left or right side, leaving her with a mild motor delay. Extensive investigations including MRI and EEG at the Hospital for Sick Children failed to reveal an etiology. A diagnosis of AHC was made and she was started on flunarizine and clonazepam, but the hemiplegic attacks continued with motor developmental delay.

An in-hospital study of oral GHB was undertaken at NYGH: starting at 10 mg/kg TID, 20 mg/kg TID, finally reaching a maximal dose of 30 mg/kg TID without adverse effects. Prolonged EEG recording with electrodes in the 10–20 system for 60 min accompany each dose escalation. The child was discharged on a maintenance dose of GHB 20 mg/kg TID and had a reduction in AHC attacks at 2 months follow-up, but she showed some motor developmental gains.

Findings: The baseline EEG pre-GHB showed diffuse beta activity and slight slowing of the background activity. At 10 mg/kg GHB, no immediate change was noted but 5 min later diffuse theta waves at 5–6 Hz appeared. The infant became drowsy with 3–4 Hz but did not sleep. At 20 mg/kg GHB, diffuse fast activity was noted, followed by theta activity, then FIRDA at 3 Hz, but no stage II sleep. At 30 mg/kg, drowsiness occurred earlier with hypernagogic hypersynchrony, FIRDA at 3 Hz at 10–15 min and stage I B sleep but no further. There was diffuse beta activity in the background and poor development of later stages of sleep.

Conclusion: GHB in the dosage range of 10–30 mg/kg orally is well tolerated, and apart from mild sedation, has little adverse

effects. The EEG changes are compatible with early drowsiness, and reached at most stage I B sleep. The efficacy of GHB in the long-term therapy of AHC and prevention of neurocognitive sequelae remains unknown.

9. Widespread and intense BOLD changes during brief focal electrographic seizures—Eliane Kobayashi, Colin S. Hawco, Christophe Grova, François Dubeau, Jean Gotman (Montreal Neurological Institute and Hospital, McGill University)

Background: Combined recording of EEG and functional magnetic resonance imaging (fMRI) has shown changes in blood oxygenation level dependent (BOLD) signal during focal interictal epileptic spikes. Due to difficult assessment of seizures inside the scanner little is known about BOLD changes during seizures.

Objectives: Describe BOLD changes related to brief focal electrographic seizures in a patient with right temporo-parietal gray matter nodular heterotopia.

Methods: The patient underwent two EEG–fMRI sessions during which several focal seizures were recorded. EEG was acquired continuously during scanning and seizure timing was used for statistical analysis. Functional maps were thresholded to disclose positive (activation) and negative (deactivation) BOLD changes.

Results: Twenty-five focal electrographic seizures were analyzed, consisting of runs of polyspikes lasting 2–6 s in the right temporal region. Activation included a large volume, involving the heterotopia and the abnormal temporo-parietal cortex overlying the nodule, with a clear maximum over the angular gyrus. Deactivation was bilateral and maximum in the occipital regions. The hemodynamic response function showed a return to baseline of the BOLD signal 30 s after seizure end.

Conclusions: The brief focal seizures resulted in high amplitude and widespread metabolic changes with BOLD responses taking 30 s to return to baseline. This suggests that such brief events could have important behavioral consequences despite absent overt manifestations. A clear focal BOLD peak was found at some distance from the main EEG discharge, raising the possibility that the seizure started in a region that did not generate a visible EEG discharge despite its superficial location.

10. Clinical significance of isolated hippocampal volume asymmetry in childhood epilepsy—P. Major[1], J.-C. Décarie[2], A. Nadeau[1], P. Diadori[1], A. Lortie[1], D. Nguyen[3], P. Cossette[1,3], L. Carmant[4] ([1]Department of Pediatrics, Neurology Division, Hôpital Sainte-Justine, Montreal, Quebec, Canada, [2]Department of Radiology, Hôpital Sainte-Justine, Montreal, Quebec, Canada, [3]Neurology Department, CHUM Hôpital Notre-Dame, Montreal, Quebec, Canada, [4]Université de Montréal, Montreal, Quebec, Canada)

Background: Hippocampal asymmetry (HA) without sclerosis is considered a precursor of mesial temporal sclerosis (MTS). The goal of this study is to define the clinical characteristics and evolution of epileptic children with isolated HA.

Methods: MRIs were reviewed blindly and HA assessed visually by one neuroradiologist. Seizure history, EEGs, risk factors and outcome were recorded.

Results: Twenty charts were reviewed. Four were excluded after MRI review. Seven boys and 9 girls were included. Fourteen had partial epilepsy and two generalized epilepsy. Interictal discharges or focal slowing were mainly ipsilateral to HA ($n=10$), but sometimes contralateral ($n=3$). Mean age at onset of the epilepsy was 6.7 years (range: 1–15). Only two individuals had a past history of febrile seizures. Unexpectedly, 11 individuals had a positive family history of seizures. Seizure control in monotherapy was achieved in the majority of patients ($n=11$, mean follow-up = 4.3 years, range 1–10).

Conclusion: The association of a positive family history of epilepsy (11/16), low incidence of febrile seizures (2/16) and benign prognosis (seizure control in monotherapy in 11/16, mean follow-up = 4.3 years, range 1–10) suggest a different clinical presentation than patients with MTS. Genetic studies of these mostly French–Canadian families should help confirm the existence of a distinct syndrome.

11. Beyond balance: The role of network structure in population dynamics—Elan Liss Ohayon[1,3], Maxim Bazhenov1, Terrence J. Sejnowski1, Hon C. Kwan[2], W. McIntyre Burnham[3] ([1]Computational Neurobiology Laboratory, Salk Institute, La Jolla, CA, USA, [2]Department of Physiology, University of Toronto, Toronto, ON, Canada, [3]University of Toronto Epilepsy Research Program, Toronto, ON, Canada)

Balance of synaptic excitation and inhibition as well as intrinsic neuronal properties are often cited as the central factors in determining the persistence of brain activity and propagation. In this study, we use computational models to demonstrate that the structure of a network, such as the level of heterogeneity in connection patterns, can be a critical feature in determining network dynamics.

To illustrate the phenomenon we simulated networks with up to 5000 spiking neurons using a difference equation based model. The networks consisted of both inhibitory and excitatory populations with inter-layer and columnar intra-layer connectivity. We then show that the inclusion of heterogeneous connectivity patterns—in the form of network boundaries, diffuse cell removal or localized cell deletion—can quantitatively and qualitatively affect network threshold response, activity duration and propagation patterns. As an example, we began with an intact homogeneous network in which the response to a localized stimulus or distributed noise was shown to dissipate quickly. Cells were then randomly removed and connectivity density lowered (p deletion = 0.3–0.7). Following the deletions, the same stimulus level now resulted in persistent activity in the form of propagating waves. As density was lowered further (p deletion = 0.7–0.9) the wave propagation patterns were progressively reduced and eventually disappeared. That is, the persistent activity remained but the network became too sparse to support waves. Spatial activity in the sparse networks tended to remain localized and settle into isolated pockets of oscillatory patterns. The variation in activity as a function of changes in network structure was thus non-monotonic.

It is important to note that the inhibitory to excitatory ratio of the connections was kept constant as were cell intrinsic properties. The model thus shows that connectivity structure can determine population activity independently of changes to inhibitory and excitatory balance. The findings suggest that architectural alterations may be important for understanding threshold drops seen in post-traumatic epilepsy. The findings are also relevant to changes in EEG seen in neurodegenerative disorders. Most importantly perhaps, network structure is clearly a critical factor in considering how the normal brain maintains the persistent activity required for cognitive processing.