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1 Anticonvulsant efects of tetrahydroprogesterone — a comparison with the anticonvulsant effects of dihydroprogesterone – McIntyre Burnham W., Deborah Lonsdale (University of Toronto Epilepsy Program and Department of Pharmacology, University of Toronto, Ontario, Canada)

Background: It is known that progesterone has anticonvulsant actions, in animals and humans. Last year we reported that progesterone's first metabolite, dihydroprogesterone (DHP), has strong anticonvulsant effects in amygdala-kindled rats, without sedation, involving suppression of the kindled amygdala focus and the generalized kindled convulsion. This year we report the effects of progesterone's second metabolite, tetrahydroprogesterone (THP), a.k.a. allopregnanolone.

Methods: Adult female Wistar rats had electrodes implanted in the right amygdala, and kindled to a criterion of 30 stage 5 seizures. Varying doses of THP were administered to each subject in randomized order, and the effects on the kindled amygdala focus and generalized kindled convulsion observed. Before each drug trial, ataxia was rated using the Loscher Scale.

Results: The generalized kindled convulsion was fully suppressed in all subjects (ED50 = 1.1 mg/kg). Ataxia (Loscher rank 2 or higher) was seen at higher doses (TD50 = 8.3 mg/kg). The therapeutic index for suppression of the generalized convulsion was 7.5. Even at the highest doses, however, the kindled amygdala focus was not suppressed.

Conclusion: THP has anticonvulsant effects, and a good therapeutic index, against generalized kindled convulsions, an animal model of tonic-clonic seizures. It has little effect, however, against the kindled amygdala focus, an animal model of complex-partial seizures. It seems to work by a different anticonvulsant mechanism than DHP.

2 Is the ketogenic diet anticonvulsant in rats? – Kirk Nylen, Jasper Clarke, Peter Abdelmalik, Sergei Likhodii, McIntyre Burnham (Department of Pharmacology, University of Toronto Epilepsy Program, University of Toronto, Ontario, Canada)

Administration of the ketogenic diet (KD) in rats has not consistently replicated the anticonvulsant effects seen clinically. Either varying methodologies between studies have caused these discrepancies, or rats don't accurately model the effects seen in humans. The present study explored these possibilities by comparing two KDs in adult rats and rat pups.

Eighty adult male rats and 75 male rat pups were fed a(n): (1) 6.3:1 (fat to protein plus carbohydrate) KD (frequently used in rat studies), (2) control diet corresponding to 6.3:1 KD, (3) 4:1 KD (a rat version of human 'classic' KD), (4) control diet corresponding to 4:1 KD, (5) ad libitum control diet. Rats were then tested using the pentylenetetrazole infusion test.

No anticonvulsant effects were observed in either rat pups or adult rats fed the 4:1 KD ($P > 0.05$). In adult rats and rat pups fed the 6.3:1 KD, a trend towards anticonvulsant effects ($P = 0.06$), and significant anticonvulsant effects were seen ($P < 0.01$), respectively. These results suggest that the anticonvulsant effects of the KD are diet- and age-dependent. The lack of the effect with the 4:1 KD, a form of 'classical' KD effective in humans, suggests that rats do not perfectly model anticonvulsant effects of the KD seen clinically.

3 The ketogenic diet. probing the anticonvulsant mechanism – Sergei S. Likhodii, McIntyre Burnham W. (Department of Pharmacology, University of Toronto Epilepsy Program, University of Toronto, Ontario, Canada)

Recent studies suggested that the ketogenic diet, which is used to control drug-resistant seizures in children, works by raising acetone in the brain. The mechanisms of acetone's anticonvulsant effects, however, remain unclear. To probe these mechanisms, we investigated structure-activity relationship of 'acetone-like' compounds.

Compounds tested differed from acetone either (1) by the length of aliphatic carbon chain; (2) by presence of –OH in place of =O group; (3) by location of =O (or –OH) group on carbon chain; (4) by presence of the branched chain, etc. The dose-response anticonvulsant effects were measured using the maximal electroshock seizure test. Toxic effects were measured using rotorod test. Compounds showing best therapeutic indices were tested for suppression of epileptic-like discharges in tetanized hippocampal slices.

We discovered that a number of 'acetone-like' compounds are potent anticonvulsants, both in vivo and in vitro. Many compounds had better therapeutic indices than valproate, an established anticonvulsant. The most striking observations were: (i) an increase in potency with the elongation of the carbon chain, and (ii) a 'cutoff' in anticonvulsant activity as the chains reach 10 or more carbons ($n = 10$). These features can be explained by the compounds binding to a pocket of fixed dimensions on a yet unidentified receptor.

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4 Do Kindled seizures cause hippocampal cell loss? – Sesath Hewapathirane D., McIntyre Burnham W. (Department of Pharmacology, University of Toronto Epilepsy Program, University of Toronto, Ontario, Canada)

Background: Whether brief seizures cause hippocampal damage is not presently clear. Kindling is an animal model of epilepsy characterized by brief seizures. The previous studies on kindling and hippocampal cell loss have reported contradictory results.

Methods: Rats were amygdala-kindled to 30 stage 5 seizures. Hippocampal tissue from kindled and control subjects were compared for: (1) cell loss, by estimating numbers using the optical fractionator method of stereological counting; (2) neuro-degeneration, using fluorojade-B staining; and (3) apoptotic stress, by measuring Bax (pro-apoptotic) and Bcl-xl (anti-apoptotic) mRNA levels via in situ hybridization.

Results: (1) No significant differences in total cell numbers were found. (2) No neuro-degeneration was evident. (3) Bax expression was significantly up-regulated, whereas Bcl-xl expression was not.

Conclusions: Kindling to 30 stage 5 seizures does not cause significant cell loss or neuro-degeneration. Increased Bax mRNA levels suggest apoptosis may be occurring. Possible explanations and implications are discussed.

5 Effect of hyperthermic seizures on total cerebral volume in rats with focal cortical dysplasia – Steve Gibbs, Morris H. Scantlebury, Caterina Psarropoulou, Lionel Carmant (Centre de recherche, Hôpital Sainte-Justine, Montréal, Québec H3S 1W3)

The association between atypical febrile seizures and mesial temporal lobe epilepsy syndrome (MTLE) is controversial. Although supported by retrospective studies, prospective studies have not established an increased risk of developing epilepsy and experimental models of prolonged febrile seizures have not resulted in spontaneous recurrent seizures or brain damage, typically found in patients with this condition. Several surgical series support another association between MTLE and cortical dysplasias suggesting a predisposing role of cortical dysplasia in the development of atypical febrile seizures.

In our laboratory we have recently confirmed that focal cortical dysplasia leads to atypical hyperthermic seizures (HS) in rats. In this study we report that after 12 days these atypical HS leads to a 7–9% loss in brain volume as compared to lesioned alone, sham-operated and naïve rats exposed to hyperthermia. Furthermore, preliminary results indicate that this reduction in cerebral volume persists into adulthood ($>P60$). In the acute period, 48 h post hyperthermia, the brain volume in lesioned rats with or without hyperthermia were 9% smaller than controls, however, there were no differences between these two groups.

Taken together these results suggest the atypical HS in lesioned rats inhibits brain growth supporting previous studies in the immature rat and more recently a report of a loss of cerebral volume in a small series of adult patients with MTLE and childhood history of atypical febrile seizures. The impact of our findings on learning and memory will be discussed.

6 Exploring ictogenesis in isolated preparations of mouse hippocampus and frontal neocortex maintained in vitro – Peter A. Abdelmalik, McIntyre Burnham W., Peter L. Carlen (University of Toronto Epilepsy Research Program, Toronto, Ontario, Canada; Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada; Toronto Western Research Institute, University Health Network, Toronto, Ontario, Canada)

Background: Seizures originating from limbic structures often have a low threshold and are frequently drug resistant. Conversely, frontal neocortex has a higher seizure threshold and is more responsive to pharmacotherapy.

Methods: We report a novel model for studying neocortical seizures using an isolated mouse neocortical block (coronal, 1000 μm) and compared to intact hippocampus isolated from the contralateral brain.

Results: Isolated mouse neocortical blocks were viable under normal ACSF perfusion for more than 3 h. Neocortical blocks were able to generate both recurrent, spontaneous seizure-like events (SLEs) and interictal-like events under low Mg^{2+} ACSF perfusion, however, with characteristics distinct from hippocampus. SLEs generated in neocortex had longer latencies to SLE onset, lower frequencies and shorter durations, observations also noted during 4-aminopyridine (4AP, 50 μM) perfusion. Under low Mg^{2+}, APV (60 μM) reversibly abolished SLEs in the neocortex, yet exacerbated them in the hippocampus. CNQX (10 μM), completely and reversibly abolished all SLE activity in both isolated preparations, yet interictal-like activity persisted in neocortex. Nifedipine (10 μM) increased spontaneous activity in both preparations.

Conclusion: Data suggest ictogenesis of brain regions may be a network phenomenon, independent of particular receptor/channel subtypes. Isolated hippocampus demonstrates increased propensity for seizure generation versus isolated neocortex, consistent with both clinical and in vivo experimental models.

7 Neurophysiological abnormalities in manganese neurotoxicity – Chen Li, Jane Shaw, Venita Jay, Paul Hwang (Neurophysiology Laboratory, Neurology, North York General Hospital, University of Toronto Epilepsy Research Program, Toronto, Canada)

Objective: To quantify neurophysiological findings in patients with high manganese serum levels.

Methods: All patients had high serum levels of manganese (Mn) measured by an independent laboratory (Royal Blue method), neurological examination by the same neurologist (PAH) and neurophysiological (NP) studies in the same laboratory, using standardised techniques: EEG, BAEP, VEP and median-nerve SEP, with normal limits set at mean ± 3SD ($P < 0.01$).

Results: Twelve male patients, aged 39–70 years, had serum Mn levels of 26.0–43.1 μM/l (normal 5.5–18.2), seen October 2000–2003, in a community-based practice of 4500 patients. Eight (67%) had Parkinsonian symptoms (tremor, rigidity, bradykinesia), six (75%) with abnormal NP: absent or delayed mn-SEP (4), absent or delayed BAEP (2), prolonged P100 in VEP (2), decreased NCV (2) or non-epileptiform EEG (1). Only two had normal NP studies. Of the four patients without Parkinsonism (25%), three had headaches and one foot-drop. NP showed decreased NCV or absent

CAP (2) and TIRDA in the EEG (1). Only one had normal neurological and NP findings.

Conclusion: This retrospective uncontrolled study suggests manganese may be neurotoxic, with selective vulnerability of the basal ganglia, and/or the large-fibre systems of the somatosensory, visual or the auditory-brainstem pathways and the peripheral nerves. If confirmed in a large controlled study, this heavy metal should be considered a neurotoxin requiring monitoring and possible therapy.

8 Postictal rage and aggression: a video-eeg study – Yankovsky A.E., Tampieri D., Dubeau F., Andermann F. (Montreal Neurological Hospital and Institute, McGill University, Montreal, Quebec)

Background: Postictal rage and aggression have been described but have rarely been documented by EEG-video recording.

Methods: We studied a patient with dramatic episodic rage and violence.

Results: A mentally retarded man had a lifelong history of seizures. He developed increasing episodic rage and aggression. Caregivers were afraid of him although there was no record of directed violence. In one of these episodes he fractured the tibia and fibula. Interictal discharges arose from both temporal areas independently. He had focal seizures with secondary generalization. Immediately after cessation of the ictal discharge he became greatly agitated with undirected aggression, screaming loudly, kicking and fighting the restraints. A videoclip will illustrate the behavior. Imaging studies showed bilateral periventricular nodular heterotopia in the lateral aspect of both temporal horns and the trigones. A search for filamin mutations is under way.

Conclusions: Increasingly frequent and severe bursts of rage and aggression were proven to be postictal. Documented attacks occurred while he was restrained and this may have been a factor in their severity. Such attacks, however, have been described while he was not restrained and these increased in severity and frequency over time. Developmental abnormalities with periventricular nodular heterotopia in the region of the trigones but also in inferomesial temporal areas are considered to be causally related to his retardation and epilepsy.

9 Development of EEG Biofeedback and Comments on its use in Neurological Disorders – Michael Thompson, Lynda Thompson (ADD Centres Ltd, 50 Village Centre Place Mississauga, Ont. L4Z 1V9)

For over a quarter century a small group of psychologists have been studying ways to do quantitative measurements of the EEG, to train the brain, and to change EEG patterns. One pioneer was Joe Kamiya, who in 1958 demonstrated that people could correctly identify when they were producing alpha waves. Then a sleep researcher, M. Barry Sterman, demonstrated that cats could be trained using *operant conditioning* to increase a specific spindle-like brain wave pattern that he named *sensorimotor rhythm (SMR)*. Closely following on this discovery was his serendipitous discovery that cats trained to increase SMR activity (12–15 Hz) were resistant to seizures caused by toxic exposure. Further experiments with humans showed that patients with epilepsy could be trained to increase SMR with a concomitant decrease in the frequency and severity of seizures. Another application of neurofeedback that has been validated with controlled research is self-regulation of the symptoms of Attention Deficit/Hyperactivity Disorder. Joel Lubar has done research concerning neurofeedback for ADD at the University of Tennessee since 1976 and has established that the theta/beta ratio is helpful in differentiating between normals and those with ADHD. More recent work has shown distinct QEEG differences in a number of clinical entities. This presentation will outline the QEEG patterns observed in ADD and in Asperger's Syndrome, relate how training is carried out, and share outcomes. An interesting case of using neurofeedback to augment traditional treatments in a woman with Parkinson's Disease and Dystonia will also be discussed.