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Marmoset model of trauma-induced epileptogenesis—Olga Bukhtiyarova, Igor Timofeev (Department of Psychiatry and Neuroscience, School of Medicine, Université Laval, Canada, CERVO Brain Research Centre, Quebec, QC, Canada)

We investigated brain electrographic activity in freely behaving marmosets before and after cortical penetrating wound. Based on visual examination of the multi-channel cortical and hippocampal LFP recordings and muscle activity, we were able to distinguish six behavioural states: active and quiet wake, an intermediate state, NREM2, SWS and REM sleep. We developed a procedure for automatic classification of states of vigilance in marmosets based on different LFP power bands and muscle tone with the use of self-organizing maps. Marmosets were typically awake during the day with few occasional naps and had 12–18 sleep cycles during night. In order to evaluate them as a model of human trauma-induced epileptogenesis, we produced cortical penetrating wound in 3 marmosets. All of them developed electrographic epileptiform activity within the first weeks that was primarily local. Its secondary generalization led to behavioural seizures that started to manifest 2–4 weeks after the onset of electrographic events.

Conclusion: Cortical penetrating wounds in marmosets trigger epileptogenesis that result in seizure onset within a few weeks. Their brain state cycle is closer to human as compared to typical laboratory animals (rodents and carnivores) that favours translation of findings in marmoset model of trauma-induced epileptogenesis to human studies.

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Accuracy and spatial properties of distributed magnetic source imaging (dMSI) techniques in the investigation of focal epilepsy patients—Giovanni Pellegrino [1,2], Tanguy Hedrich [3], Manuel Porras-Bettancourt [1], Jean-Marc Lina [4,5], Christophe Grova [3,6], Eliane Kobayashi [1] ([1] Neurology and Neurosurgery Dpt., Montreal Neurological Institute, McGill University, Montreal, QC, Canada, [2] IRCCS Fondazione San Camillo Hospital, Venice, Italy, [3] Multimodal Functional Imaging Lab, Biomedical Eng. Dpt., McGill University, Montreal, QC, Canada, [4] Departement de Genie Electrique, Ecole de Technologie Superieure, Montreal, Quebec, Canada, [5] Centre De Recherches En Mathematiques, Mntreal, Quebec, Canada, [6] Physics Department and PERFORM Centre, Concordia University, Montreal, Quebec, Canada)

Introduction: Source localization of interictal epileptic discharges (IEDs) is clinically useful in the presurgical workup of epilepsy patients. Recently, we have demonstrated that distributed magnetic source imaging (dMSI) has better accuracy than clinically approved equivalent current dipole method (ECD). Here, we aimed to compare the performance of four different dMSI techniques: Minimum Norm Estimate (MNE), dynamic Statistical Parametric Mapping (dSPM), standardized Low-Resolution Electromagnetic Tomography (sLORETA) and coherent Maximum Entropy on the Mean (cMEM, an entropy-based technique).

Methods: We analyzed dMSI results of 206 IEDs derived from MEG recordings in 28 focal epilepsy patients who had a well-defined focus determined through intracranial EEG, epileptogenic MRI lesions or surgical resection. dMSI accuracy and spatial properties were quantitatively estimated as: (a) minimum distance between the source peak and the focus; (b) within-subject reproducibility; (c) spatial dispersion of the source map outside the focus; (d) extension of cortical map; (e) effect of thresholding on map size and properties.

Results: Distance between the map peak and epilepsy focus as well as within subject reproducibility were clinically comparable across methods (median distance from the focus around 1 cm). Spatial dispersion was significantly lower for cMEM. cMEM maps display typically higher contrast between the source maximum and surrounding regions, being therefore less sensitive to map thresholding.

Conclusions: All dMSI techniques under investigation provided excellent performance in localizing the epileptic focus. cMEM provides the lowest amount of spurious activity, while obtaining similar localization accuracy compared to other techniques. dMSI techniques currently available for clinical use have the potential to significantly improve identification of intracranial EEG targets and to guide surgical planning.

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Role and metabolism of omega-6 linoleic acid in the brain—Ameer Y. Taha (Department of Food Science and Technology, University of California Davis, CA, USA)

Omega-6 linoleic acid (LA) has become ubiquitous in our diets due to agricultural shifts towards high LA soybean and corn oils, resulting in a 3- to 5- fold increase in LA intake over the past few decades. Despite being a dietary stipulate, LA has been considered a benign fatty acid in the brain because of its low concentration (<2%) relative to other polyunsaturated fatty acids such as arachidonic and docosahexaenoic acid. LA, however, crosses the blood brain barrier at a rate comparable to other polyunsaturated fatty acids. It is also a precursor to oxidized linoleic acid metabolites

(OXLAMs) known to regulate signaling in peripheral tissue. The role of LA or its metabolites (OXLAMs) in the brain are unknown. The present series of rodent experiments tested the hypothesis that LA entering the brain is converted into OXLAMs that regulate neuronal signaling. We found that increasing dietary LA increased the incorporation rate of deuterated LA into the brain, and its conversion into OXLAMs. 13-hydroxyoctadecadienoic acid (13-HODE), one of the main OXLAMs found in the brain, increased somatic paired pulse facilitation when applied to hippocampal slices at 100 nM. LA itself did not alter somatic neurotransmission. These findings provide evidence that excess dietary LA increases brain LA incorporation and conversion into OXLAMs, and that 13-HODE (an abundant OXLAM in the brain) regulates neurotransmission. The potential contribution of other OXLAMs to brain network activity merits further investigation.

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Kleine-Levin Syndrome: Familial or sporadic?—Boris Yakubov [1,3], Colin Shapiro [1,2,3], Dragana Joven [2], Inna Voloh [2], Paul Hwang [2,4] ([1] International Sleep Clinic (WPSHC), Canada, [2] Youthdale Child and Adolescent Sleep Centre, Canada, [3] Department of Psychiatry, University of Toronto, Canada, [4] University of Toronto Epilepsy Research Program, Canada)

Introduction: Kleine-Levin Syndrome (KLS) is a rare neurological disorder characterized by recurrent periods of excessive hypersomnolence and altered behavior. It mainly affects adolescents, but younger children and adults may be diagnosed with this syndrome as well. At the onset of symptoms patients may sleep for most of the day and night, which significantly affects their daily activities. Symptoms of KLS may last up to 10 years or more. Specific causes of KLS are not known, but hypothalamic or circadian dysfunction could be a possibility. Viral infections, as well as concerns of metabolism of serotonin and dopamine are suggested factors as the causes. Additionally, a link to the gene LMOD3 on chromosome 3 was speculated to be the cause in one study.

Case report: A 19-year-old male started to experience severe hypersomnolence when he was approximately 14 years of age. His symptoms persisted for over a year. Prior to hypersomnolence, this patient was experiencing symptoms of insomnia. At that time, it was thought that he may have phase delay syndrome. He had a history of migraines without auras, a learning disability due to attention deficit hyperactivity, asthma, and several bouts of strep throat. The patient was born full term with a birth weight of 9 lbs, 5 oz. When the patient begun to experience hypersomnolence, studies that were conducted included EEG as well as MRI of the head with close-up views of the hypothalamus. He was also referred to the Youthdale Child and Adolescent Sleep Centre where polysomnography with MLST was performed to rule out sleep abnormalities, including narcolepsy and phase delay syndrome.

Results: EEG studies in 2014 and 2015 showed no abnormalities. MRI of the brain suggested heterogeneous signal intensity in the pituitary gland. During overnight PSG he slept for 12 h and had 2 SOREM periods in the following multiple sleep latency tests. This led to the potential diagnosis of narcolepsy, but he did not have primary symptoms of cataplexy, hypnogogic hallucinations, or sleep paralysis. He felt tired and had severe bouts of sleep. The video-EEG with subtemporal recording was normal during waking, SWS, and REM sleep.

Discussion: This case is unique as the diagnostic studies with vague results do not provide him with a specific diagnosis. This patient's symptoms, therefore, suggested that he may have KLS; however, this was hard to prove due to the rarity of this condition and a lack of specific guidelines for diagnosis. In this case, it became important to start looking at the possibility of certain gene mutations, including the gene LMOD3, as there has been a link to KLS. A few studies have found that a possible Jewish predisposition is present, even though the majority of cases are sporadic. Continued research in this field with more genetic studies is important in order to better understand the etiology of KLS.

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The effects of 5a-dihydroprogesterone and benzyl alcohol in amygdala-kindled seizures—Yinhao Violet Wu, W. McIntyre Burnham (The University of Toronto, Department of Pharmacology and Toxicology, Toronto, Canada)

5a-dihydroprogesterone (DHP), the primary metabolite of progesterone, has anti-seizure properties. The present study investigated the time-course of the anti-seizure effects of 5a-dihydroprogesterone, injected via the IP route, in an animal model of human drug-resistant seizures – the amygdala-kindling model.

Female, Wistar amygdala-kindled rats were injected intraperitoneally (I.P.) with 30 mg/kg of DHP, and the suppression of focal electrographic seizures and secondarily generalized convulsions was tested from 10 to 150 min post-injection. DHP was dissolved in the "benzyl vehicle" (benzyl alcohol: benzyl benzoate: cottonseed oil, 1.5:1.5:7, v:v:v), DHP in the benzyl vehicle demonstrated good anti-seizure effects at two time points: (1) immediately (10–20 min) after injection, and (2) at about 130 min after injection. Both generalized and focal seizures were suppressed at the early time point, but only generalized seizures were suppressed at 130 min. Ataxia was seen at the earlier time point, but not at the later time-point.

When a vehicle control was done, we observed both focal and generalized seizure suppression at the early time point (10–20 min) in the absence of DHP. A subsequent examination revealed that benzyl alcohol was the only active ingredient in the benzyl vehicle, and that it has clear anti-seizure effects. No seizure suppression was seen with benzyl alcohol at later time points.

In conclusion, the anti-seizure effects seen shortly after injection may relate to either DHP or benzyl alcohol, whereas the seizure suppression seen at later time points seems to relate to DHP, or perhaps a DHP metabolite. A future study might attempt to establish a time-course for DHP metabolism in the rat and to determine what compound relates to these late-developing effects.

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The effects of CBD and THC in animal models of depression and anxiety—Junhan Liu, McIntyre Burnham (Department of Pharmacology and Toxicology, University of Toronto, Canada)

Objectives: Epilepsy patients frequently suffer from psychiatric comorbidities, such as depression and anxiety, which seriously affect their quality of life. CBD has been reported to have not only anti-seizure effects, but also to have possible anxiolytic and antidepressant effects. Thus, CBD might treat not only seizures but also the comorbidities associated with seizures. The present study was designed to test the effects of THC, CBD and a combination of CBD and THC (15:1 ratio) in mice models of anxiety (the elevated plus maze EPM) and depression (the forced swim test FST).

Methods: EPM Adult, male CD1 mice (30–35 g) were injected i.p. with CBD (0, 3, 6, 12, 24, 48, 96 mg/kg), THC (0, 0.2, 0.4, 0.8, 1.6,

3.2, 6.4 mg/kg), CBD + THC (0, 3 + 0.2, 6 + 0.4, 12 + 0.8, 24 + 1.6, 48 + 3.2, 96 + 6.4 mg/kg) or diazepam (positive control, 0, 2.5 mg/kg). They were then tested in the EPM for 5 min. FST Adult, male CD1 mice (30–35 g) were injected i.p. with CBD (0, 7.5, 15, 30, 60, 120 mg/kg), THC (0, 0.5, 1, 2, 4, 8 mg/kg), CBD + THC (0, 7.5 + 0.5, 15 + 1, 30 + 2, 60 + 4, 120 + 8 mg/kg) or imipramine (positive control, 0, 30 mg/kg). They were tested in the FST (6 mins) or in open field arena (60mins). CBD was injected 60mins prior to testing and THC was tested 30mins prior to testing. Mice were tested only once. N = 10–15 for each dose.

Results: CBD did not have significant effects in either test at any dose. THC caused a significant increase in the time spent in the open arms of the EPM at 3.2 and 6.4 mg/kg, and significantly decreased immobility time in the FST at 2 mg/kg without affecting open field activity. The combination of CBD and THC was no different than THC alone.

Conclusions: CBD did not show anxiolytic or antidepressant effects in our animal models. THC, however, had both anxiolytic and antidepressant effects at some doses. Conceivably, a combination of CBD and THC might be useful in patients with combined seizures and psychiatric comorbidities.

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The behavioral effects of CBD and THC in mouse models of psychosis—C.K. Li, C.A. Mielnik, A.J. Ramsey, R.A. Ross, W.M. Burnham (Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada)

Approximately 10% of the patients with long-term temporal-lobe epilepsy develop psychotic symptoms, which are known as the "psychosis of epilepsy" (POE). The relationship between the two disorders remains elusive, although they are believed to share similarities in underlying mechanisms and substrates.

Previous studies have reported anti-psychotic properties of cannabidiol (CBD) and pro-psychotic properties of Δ9-tetrahydrocannabinol (THC) in both animals and human patients. The present study investigated the behavioral effects of CBD (60 and 120 mg/kg), THC (4 mg/kg) and a combination of CBD and THC at a 15:1 ratio (60:4 mg/kg) in two mouse models of psychosis – GluN1KD and DATKO mice. The open field locomotion test (OFT) and the pre-pulse inhibition test (PPI) were used.

In the OFT, CBD had no significant effect in either mouse model, whereas THC significantly decreased locomotion in both models, (accompanied by an observed impairment in ambulation). In combination, CBD increased THC's effects in GluN1KD mice and decreased THC's effects in DATKO mice. In the PPI test, 120 mg/kg of CBD significantly improved PPI in GluN1KD mice. Testing in DATKO mice is still in progress.

The behavioral impairments seen in the two mouse models are consistent with other animal models of psychosis. The effects of CBD and THC, however, do not match the prior literature.

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Dose response effects of the cannabinoids as anti-seizure drugs in amygdala kindled rats—M. Fallah, W.M. Burnham (Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada)

Background: Focal Impaired Awareness Seizures of temporal lobe origin (FIAS, also called "complex partial" seizures) are the most common seizures in adults, and are typically drug resistant. Management of FIAS is clinically challenging, and new interventions may be of use to achieve seizure freedom in these patients. The amygdala-kindling model is a pre-clinical model of FIAS with secondary generalization.

Objective: To assess the efficacy and safety of cannabidiol (CBD) alone, Δ9-tetrahydrocannabinol (THC) alone, and a combination of CBD and THC (15:1) in suppressing generalized and focal seizures in the amygdala-kindled rat.

Methods: Fully kindled, Sprague–Dawley rats with bipolar electrodes implanted in the right amygdala were given intraperitoneal injections of either CBD (Dose: 0–320 mg/kg), THC (Dose: 0–80 mg/kg), or a combination of CBD and THC (15:1 ratio). Suprathreshold stimulation was given after injection (CBD 2 h, THC 1 h), and efficacy assessed using stereo-EEG and the Racine scale.

Results: CBD alone suppressed generalized seizures (ED50: 80 mg/kg) and focal seizures (ED50: 320 mg/kg) in the kindling model at sub-toxic doses. THC alone also suppressed generalized (ED50: 30 mg/kg) and focal seizures (ED50: 30 mg/kg), but only at doses that produced psychotoxic effects (present above 10 mg/kg). The addition of a low dose of THC to CBD (15:1) left-shifted the dose-response curve for CBD, producing lower ED50s for both generalized (ED50: 40 + 2.66 mg/kg) and focal seizures (ED50: 40 + 2.66 mg/kg). No toxicity was seen at these doses of THC.

Conclusion: CBD and THC both have anti-seizure properties in the amygdala kindling model, although THC acts only at psychotoxic doses. The addition of small (subtoxic) amounts of THC greatly improves the efficacy of CBD. A combination of CBD and THC may be useful in the clinical management of FIAS.

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