seen in wild type mice was significantly attenuated in TRPV1 KO mice. Brain CBD concentrations were consistent with those required for TRPV1 activation and desensitisation irrespective of genotype.

CBD inhibits the equilibrative nucleoside transporter 1 (ENT1), reducing adenosine reuptake. The increase in extracellular adenosine reduces hyperexcitability and neurotransmission. CBD inhibited [^{3}H] adenosine uptake into rat cortical synaptosomes at low micromolar concentrations.

Conclusions: While the precise mechanisms by which CBD exerts its anticonvulsant properties in humans remain unknown, growing preclinical evidence suggests CBD reduces neuronal hyperexcitability through a unique multimodal mechanism of action. CBD antagonises GPR55 at excitatory synapses, desensitises TRPV1 channels and inhibits adenosine reuptake.

Funding: GW Research Ltd.

doi:10.1016/j.yebeh.2019.08.009

Epilepsy & Behavior 101 (2019) 106735

Drug-drug Interaction Studies with Coadministration of Cannabidiol (CBD) and Clobazam, Valproate, Stiripentol or Midazolam in Healthy Volunteers and Adults with Epilepsy

David Critchley[a], Jerzy Szaflarski[b], Philip Patsalos[c], Barry Gidal[d], Kevan VanLandingham[e], Gilmour Morrison[a]
[a]*GW Research Ltd, Cambridge, UK*
[b]*Department of Neurology and University of Alabama at Birmingham Epilepsy Center, University of Alabama at Birmingham, USA*
[c]*Institute of Neurology, University College London, London, UK*
[d]*School of Pharmacy, University of Wisconsin-Madison, Madison, USA*
[e]*Greenwich Biosciences, Inc., Carlsbad, USA*

Background: Drug-drug interactions (DDIs) between cannabidiol (CBD) and commonly used antiepileptic drugs (AEDs) is of clinical interest since it is anticipated that CBD will be used concomitantly with other AEDs. We present a summary of current understanding of DDIs when CBD is coadministered with clobazam (CLB), valproate (VPA), stiripentol (STP) or CYP3A4 substrate.

Methods: Effects of multiple-dose CBD on steady-state pharmacokinetics (PK) of CLB, N-desmethyl clobazam (N-CLB), VPA, 2-propyl-4-pentenoic acid (4-ene-VPA) and STP, and multiple-dose CLB, VPA and STP on steady-state PK of CBD and metabolites were evaluated in healthy volunteers. Effects of multiple-dose CBD on steady-state PK of CLB, N-CLB, VPA and 4-ene-VPA were evaluated in patients with epilepsy. The effect of CBD on CYP3A4 activity was evaluated in healthy volunteers using midazolam (MDZ) as a probe. In all studies, GW Pharmaceuticals' formulation of plant-derived highly purified CBD in oral solution (100 mg/mL) was uptitrated over 10 days to 750 mg twice daily in healthy volunteers (20 mg/kg/day for a 75 kg subject) or 20 mg/kg/day in patients.

Results: Concomitant CBD had no relevant effect on CLB exposure but increased exposure to its active metabolite, N-CLB, in healthy volunteers (3.4 fold) and patients (2.6 fold). Conversely, concomitant CLB increased CBD (by 30%) and its active metabolite, 7-OH-CBD (by 47%). Concomitant CBD had no effect on VPA or 4-ene-VPA, and slightly increased exposure to STP (by 55%). Concomitant VPA or STP did not alter CBD or its metabolites. CBD had no effect on MDZ clearance. CBD demonstrated a safety profile consistent with previous randomised placebo-controlled trials.

Conclusions: Combination of CBD with CLB resulted in a bi-directional DDI that increased levels of active metabolites of both compounds. There was no evidence of a DDI between CBD and VPA, or any effect of CBD on CYP3A4 activity (MDZ). The slight increase of exposure to STP when coadministered with CBD is not expected to result in a clinically important DDI.

Funding: GW Research Ltd.

doi:10.1016/j.yebeh.2019.08.010

Epilepsy & Behavior 101 (2019) 106736

Acute reduction of the Extracellular Trans-Synaptic Protein LGI1 increases network excitability

Eleonora Lugarà, Marco Leite, Elodie Chabrol, Gabriele Lignani, Matthew C. Walker
University College London, London, United Kingdom

Autoantibodies against LGI1 have been detected in the serum of adult patients with limbic encephalitis, seizures and status epilepticus. It is not clear if the seizures are generated by inflammation due to the antibodies or through a direct effect of the antibodies on LGI1. LGI1 (Leucine Rich Glioma Inactivated 1) is a secreted trans-synaptic protein which interacts presynaptically with Kv1.1 potassium channels and ADAM23, a membrane-anchored protein with no catalytic effect. Postsynaptically, LGI1 influences AMPA and NMDA receptors through a direct link with the ADAM22 adhesion protein. Mutations in the gene encoding LGI1 lead to temporal lobe epilepsy in humans and animal models.

We, therefore, asked if an acute reduction in LGI1 was sufficient to increase network excitability and promote seizure activity.

For this purpose, we chose and validated a silencing RNA (shRNA) against LGI1. In neuronal cultures and in *ex vivo* granule cells, shRNA against LGI1 increased neuronal firing. Local field potential (LFP) of *ex vivo* slices after injection of shRNA-LGI1 in the hippocampus, revealed an increase in the facilitation of mossy fibers to CA3 pyramidal cell neurotransmission. Application of Kv1 family blocker, alpha-dendrotoxin, occluded the increased facilitation in shRNA-LGI1 injected mice.

These results indicate that an acute reduction in LGI1 is sufficient to increase neuronal network excitability. Specifically, acutely decreasing LGI1 protein affects synaptic excitability and short-term plasticity in DG-CA3 hippocampal circuitry.

doi:10.1016/j.yebeh.2019.08.011

Epilepsy & Behavior 101 (2019) 106737

Argonaute-2 sequencing of rodent status epilepticus models identifies multiple microRNA targets for seizure suppression

Gareth Morris[a,b,c], Morten Veno[d], Cristina Reschke[a,b], Sebastian Bauer[e,f], Yan Yan[d], Tobias Engel[a,b], R. Jereon Pasterkamp[g], Jochen H.M. Prehn[a,b], Stephanie Schorge[c], Felix Rosenow[e,f], Jorgen Kjems[d], David C. Henshall[a,b]
[a]*FutureNeuro Research Centre, Dublin, Ireland*
[b]*Royal College of Surgeons in Ireland, Dublin, Ireland*