**Assessing Cannabidiol effects in two genetic models of epilepsy: pharmacological, behavioral, and electrophysiological analyses**

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**Abstract**

**Introduction:** Despite the increased number of antiseizure drugs, one in three patients with epilepsies cannot have their seizures under control using the classical pharmacological medication. Cannabidiol (CBD), a phytocannabinoid present in *Cannabis sp.* plants, is an emergent and promising therapy with antiseizure effects in humans and preclinical models, but nothing is known about CBD effects in genetic models of epilepsies. Here, we assessed CBD dose-response and time-course effects in two genetic models of epilepsies. The Genetically Epilepsy Prone Rats (GEPR-3s) is an audiogenic strain susceptible to generalized tonic-clonic seizures (GTCS) in response to intense sound stimulation (audiogenic seizures, AGS), but during the chronic protocol of AGS (audiogenic kindling, AK), GEPR-3s can develop kindled limbic seizures. The WAG/Rij is a genetic model of absence epilepsy, usually used to modeling childhood epilepsy, with animals expressing hundreds of cortical spike-and-wave discharges (SWDs) in a single day. **Methods:** GEPR-3s and WAG/Rijs were submitted to within-subject tests, receiving intraperitoneal injection (ip.) of CBD (1, 10, 50, and 100 mg/kg) and vehicle (Protocol #2016-1184). In GEPR-3s, seizures were induced by intense acoustic stimulation (120 dB) applied by an electric bell into the acoustic chamber. Immediately after a baseline AGS session, CBD or vehicle was administered; GEPR-3s were submitted to AGS test sessions at 2, 4 and 6 h after ip. CBD. Animals’ behavior was recorded for behavioral analysis. WAG/Rij rats were submitted to stereotaxic surgery for bilateral implantation of 6 cortical electrodes: 2 over frontal cortex, 2 over posterior neocortex, and 2 over the cerebellum (ground and reference). Immediately after ip. CBD or vehicle, WAG/Rijs were submitted to 6 h of continuous EEG recording. EEG signal (1kHz) was filtered (1-50 Hz) and the SWDs mean duration, SWD frequency, and total power frequency were measured. **Results:** In the GEPR-3s, CBD dose dependently (50 and 100 mg/kg) attenuated GTCS, reducing seizure severity index, tonic-clonic seizure duration and total seizure duration (*p*s<0.05). In kindled GEPR-3s with consistent and severe limbic seizures, CBD 10 mg/kg attenuated limbic seizure expression, reducing seizure severity (*p*<0.05). The most potent CBD antiseizure effects in GEPR-3s were observed at 2 h after ip. CBD (*p*<0.05), but total seizure duration remained reduced for at least 6 h after CBD (*ps*<0.05). In WAG/Rijs, a U-shape effect was detected, with CBD 1 and 100 mg/kg reducing SWDs mean duration (*p*s<0.05); the lower dose presented more potent and longer effects, attenuating SWDs at 2 and 3 h after ip. CBD (*ps*<0.05). **Conclusion:** Different CBD doses were effective to control different types of seizures in genetic models of epilepsy. Tonic-clonic and limbic kindled seizures were attenuated in GEPR-3s and SWDs mean duration were reduced in WAG/Rijs. These data support CBD use for epilepsy.

**Funding:** CAPES, (Finance code 001); CAPES-Print (Process no. 88887.370299/2019-00); National Institute of Neurological Disorders and Stroke – USA (R01NS097762).