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Perinatal neuroprotection of cannabidiol-treated developing rats after repeated bicuculline-induced seizures

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Introduction: Seizures represent a frequent adverse neurological event in newborns, causing brain damage with long-lasting impairment of cognition and behavior[1]. Since cannabidiol (CBD) has demonstrated neuroprotection in experimental neonatal hypoxic-ischemic brain damage[2], our aim was to test whether early CBD treatment improves long-term neuroprotective outcome of developing rats exposed to bicuculline-induced seizures.

Method: Rat pups (P5) received bicuculline as seizure inductor during three consecutive days at 2-4 mg/kg intraperitoneal dose[3]. Pups were randomized to receive placebo solution (VEH group) or CBD (GW Research, Cambridge UK) at 1, 10 and 100 mg/kg/day for 3 days (CBD1, CBD10, CBD100 groups). Pups without seizure or drug treatment were used as reference (SHAM group). Brain damage was assessed at juvenile stage (P37) in function of neuropathological score[4] (hippocampus and cortex), electroencephalography and cognitive deficit (sensori-motor tests: RotaRod, cylinder rearing test; learning & memory tests: T-maze, novel object recognition). Data are given as mean±SEM (sample size). Analysis was performed using Kruskal-Wallis test with Dunn's correction.

Results: Data of P37 rats with seizure brain damage and CBD treatment are summarized in table 1.

(a) $p<0.05$ vs. SHAM; (b) $p<0.05$ vs. VEH; (c) $p<0.05$ vs CBD1; (d) $p<0.05$ vs CBD10

Table 1	SHAM	VEH	CBD1	CBD10	CBD100
Neuropathological score: hippocampus	0.4±0.3 (10)	2.1±0.2[a] (10)	1.9±0.2[a] (10)	1.5±0.2[a,b] (10)	0.6±0.3[b,c,d] (10)
Neuropathological score: cortex	0.4±0.3 (10)	2.4±0.3[a] (10)	2.3±0.3[a] (10)	1.9±0.3[a] (10)	0.8±0.2[b,c,d] (10)
Electroencephalography (µV)	18±1 (10)	15±1[a] (20)	15±2 (20)	16±2 (20)	17±2 (20)
Rotarod: latency to fall (sec)	259±12 (10)	189±14[a] (20)	207±10[a] (20)	216±21[a] (20)	234±9[b,c] (20)
Cylinder rearing test: preference for left (%)	-0.3±0.5 (10)	1.8±1.9 (20)	-0.3±1.4 (20)	0.9±2.6 (20)	0.5±1.4 (20)
T-maze: correct response (%)	64±8 (10)	36±9[a] (20)	43±10[a] (20)	50±5 (20)	52±5[b] (20)
Novel object recognition: discrimination index	0.52±0.02 (10)	0.40±0.04[a] (20)	0.41±0.04[a] (20)	0.47±0.02[a,b] (20)	0.50±0.02[b,c] (20)

Bicuculline-treated pups showed tonic-clonic seizures after 10 min, which continued for 1.5- to 2 hours. VEH group developed a long-term bicuculline-induced functional impairment, as observed in the neuropathology, electroencephalography and neurobehavioral tests. CBD treatment partially reversed neurophysiological and neurofunctional sequelae of seizures.

Conclusion: Bicuculline-induced repetitive seizure in neonatal period produced a long-term functional impairment, which was evident at juvenile stage. Although, the bicuculline model did not induce significant alterations compared to sham for some of the parameters, a clear neuroprotective role of CBD was present at

100 mg/kg, maintaining structural and functional brain parameters (histology, learning, memory, motor coordination). Also, limited improvements were observed at 10 mg/kg CBD dose.

References:

1. Ronen GM *et al*. (2007). *Neurology* **69**: 1816-1822.
2. Alvarez FJ *et al*. (2008). *Pediatr Res* **64**: 653-658.
3. Doriat JF *et al*. (1998). *Brain Res* **800**: 114-124.
4. Pazos MR *et al*. (2012). *Neuropharmacology* **63**: 776-783.