Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol17Issue1abst002P.pdf

Long-term effects of treatment with hypothermia and cannabidiol in developing rats with hypoxic-ischemic brain injury

F. J. Alvarez[1], H. Lafuente[1], A. A. Alvarez[2], M. Revuelta[2], O. Arteaga[2], W. Hind[3], E. Hilario[2], J. Martinez-Orgado[4]. [1]Biocruces Institute, Cruces University Hospital, Barakaldo, Spain, [2]Cell Biology and Histology, University of the Basque Country, Leioa, Spain, [3]GW Research, Histon, Cambridge, United Kingdom, [4]Instituto del Niño y del Adolescente (INA), Hospital Clínico "San Carlos" - IdISSC, Madrid, Spain.

Introduction: Hypothermia is the standard treatment for hypoxic-ischemic (HI) newborns, but many treated infants present adverse long-term neurologic outcomes. Cannabidiol (CBD) could act through complementary mechanisms, thus improving the long-term outcomes in rats with experimental HI injury when used in combination with hypothermia[1].

Method: 7-day old rats (P7) underwent HI injury[2] and were randomized to receive normothermia (N) or hypothermia[3] (H), as well as drug treatment with CBD (GW Research, Cambridge UK) 1 mg/kg (C) or its vehicle (V). Animals without brain injury or drug treatment were used as normothermic and hypothermic sham controls (NS, HS). Brain injury was assessed one month later[4] (P37) by infarct volume percentage, neuropathological score, glutamate/N-acetyl-aspartate and N-acetyl-aspartate/choline ratios (excitotoxicity and motor outcome), electroencephalography and cognitive deficit (sensori-motor, learning & memory). Data are given as mean ± SEM (n). Analysis was performed using the non-parametric Kruskal-Wallis test with Dunn correction.

Results: Structural, functional and cognitive data from juvenile animals (P37) after treatments are summarized in table 1.

(a) $p<0.05$ vs. NV group; (b) $p<0.05$ vs. NC group; (c) $p<0.05$ vs HV group

Table 1	NS group	NV group	NC group	HS group	HV group	HC group
Infarct volume percentage (%)	0.0 ± 0.0^{a} (5)	22.2 ± 0.5 (5)	14.3 ± 0.3^{a} (5)	0.0 ± 0.0^{c} (5)	$17.2\pm0.4^{a,b}$ (5)	$10.7\pm0.2^{a,b,c}$ (5)
Neuropathological score: hippocampus	0.4 ± 0.3^{a} (10)	4.0 ± 0.4 (10)	2.5 ± 0.3^{a} (10)	0.2 ± 0.2^{c} (10)	3.2 ± 0.2^{a} (10)	$1.4\pm0.3^{a,b,c}$ (10)
Electroencephalography (µV)	19 ± 1^{a} (10)	10 ± 1 (10)	17 ± 2^{a} (10)	19 ± 1^{c} (10)	14 ± 1^{a} (10)	$17\pm1^{a,c}$ (10)
Glu/NAA ratio	1.2 ± 0.1^{a} (5)	1.8 ± 0.1 (5)	1.2 ± 0.2^{a} (5)	1.0 ± 0.2 (5)	1.0 ± 0.1^{a} (5)	1.0 ± 0.1^{a} (5)
NAA/Cho ratio	8.5 ± 0.1^{a} (5)	3.0 ± 0.2 (5)	4.4 ± 0.6^{a} (5)	9.6 ± 0.1^{c} (5)	$8.2\pm0.2^{a,b}$ (5)	$9.8\pm0.3^{a,b,c}$ (5)
Rotarod: latency to fall (sec)	259 ± 12^{a} (10)	95 ± 13 (10)	217 ± 22^{a} (10)	262 ± 10^{c} (10)	$152\pm14^{a,b}$ (10)	$218\pm5^{a,c}$ (10)
T-maze: correct response (%)	64 ± 8^{a} (10)	30 ± 5 (10)	52 ± 10^{a} (10)	66 ± 7^{c} (10)	37 ± 4 (10)	$56\pm5^{a,c}$ (10)

NV group developed a long-lasting functional impairment, as observed in infarct volume, neuropathology, electroencephalography and neurobehavioral tests. NC and HV groups showed improvements, optimized in HC group (combined therapies).

Conclusion: CBD administration to HI newborn rats led to a long-lasting neuroprotection in normothermia, but additional beneficial effects were observed when CBD was given in combination with hypothermia. The study suggests that CBD in combination with hypothermia may improve long-term neurologic outcomes.

References:

1. Lafuente H *et al*. (2016). *Front Neurosci* **12**: 323.
2. Fernandez-Lopez D *et al*. (2007). *Pediatr Res* **62**: 255-260.
3. Thoresen M *et al*. (1996). *Arch Dis Child* **74**: F3-9.
4. Pazos MR *et al*. (2012). *Neuropharmacology* **63**: 776-783.