XIX CONGRESO de la SEBC
BOADILLA DEL MONTE (Madrid)
26, 27, 28 y 29 de octubre de 2021

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URB447-induced neuroprotection targets caspase-3 activation and apoptosis after neonatal ischemic brain injury

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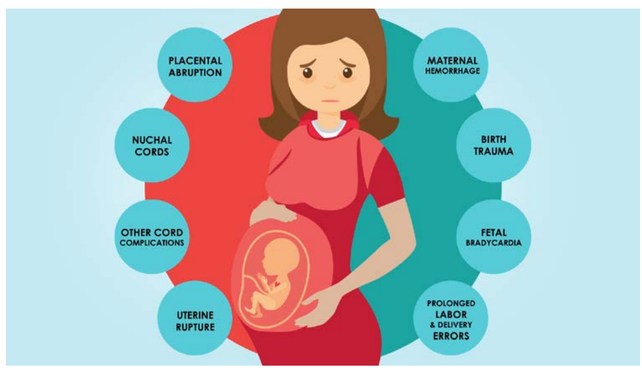
Introduction

In the management of newborn hypoxic-ischemic (HI) encephalopathy, any neuroprotective strategy must act on several factors, mainly on excitotoxicity, oxidative stress and inflammation. We wanted to explore if the simultaneous modulation of cannabinoid CB1 and CB2 receptors could induce a neuroprotective effect after hypoxic-ischemic brain damage in newborn rats.



Methods

Postnatal day 7 (P7) Wistar pups underwent unilateral ligation of the right common carotid artery and later hypoxia (8% O2/92%N2) for 2.5 h to induce HI brain injury. Some animals received 1 mg/kg i.p. of the cannabinoid URB447 3h after HI (HI+URB447, n=16) or the corresponding volume of vehicle (HI+VEH, n=16). Animals without ischemia nor hypoxia served as controls (Sham, n=16). Pups were sacrificed at 24h (P8) for biochemical analyses or at 7d (P14) for brain histology.

Results

On P14, an extensive cell loss was observed in both the cerebral cortex and hippocampus after HI (Fig. 1), with surviving cells showing dark, pyknotic neurons, most being TUNEL positive (Fig. 2). In the HI-URB447 group, Nissl-stained cells were in higher amounts compared to the HI group (Fig. 3), and showed clearer cell outlines and compact structures with few TUNEL-positive cells. At 24h, URB447 significantly reduced caspase-3 activation after neonatal HI (Fig. 4).

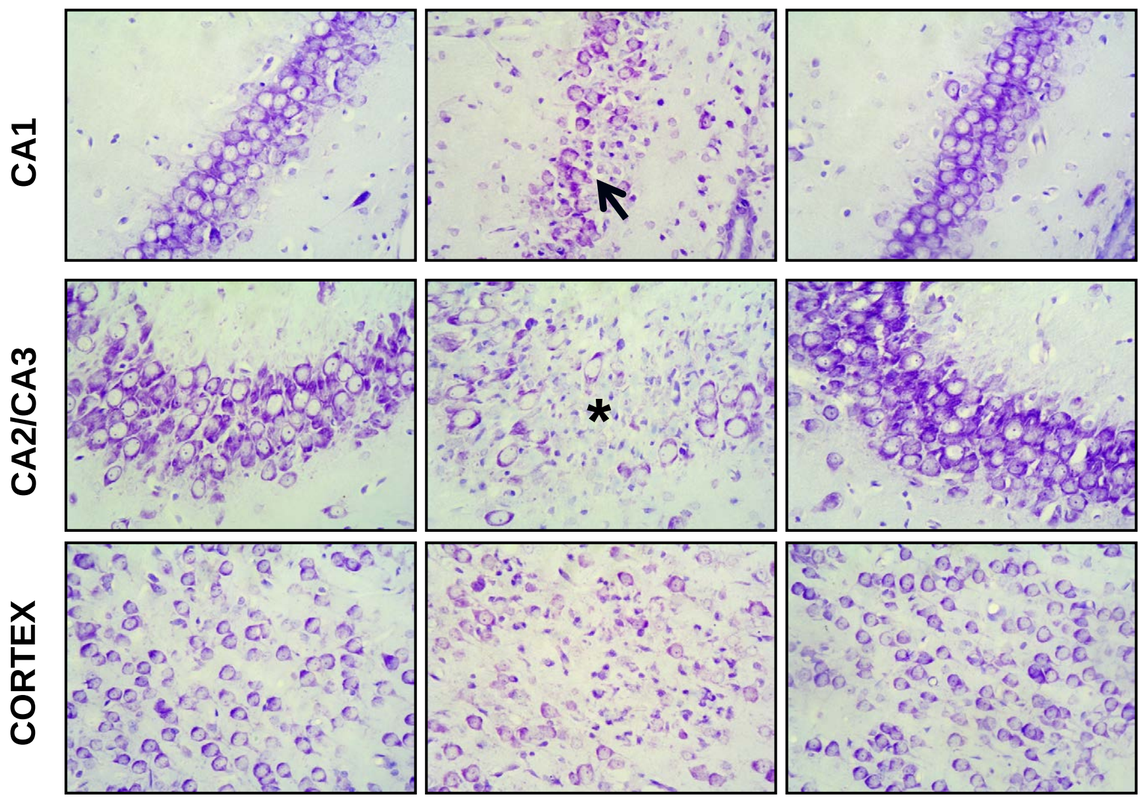


Figure 1. Nissl staining revealing extensive cell death after HI (arrow and asterisk). Well preserved neurons in Sham and HI+URB447.

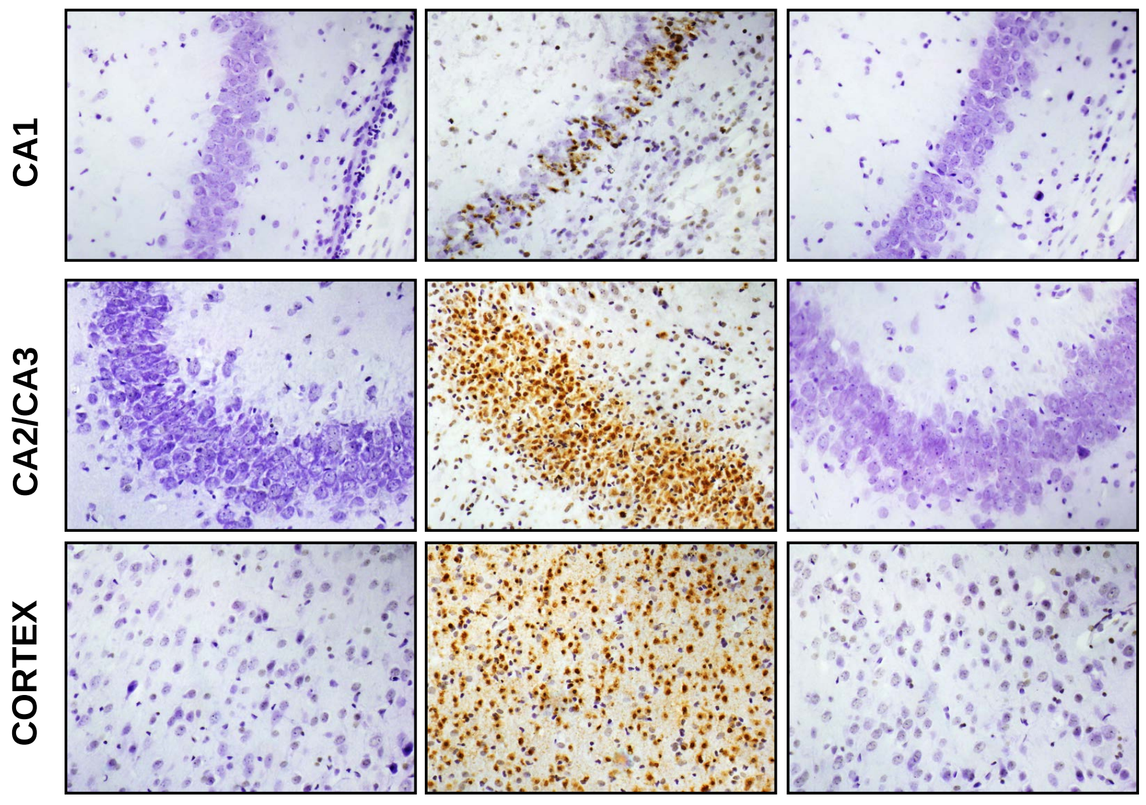


Figure 2. TUNEL immunohistochemistry revealing DNA fragmentation after HI and reduction after URB447 administration.

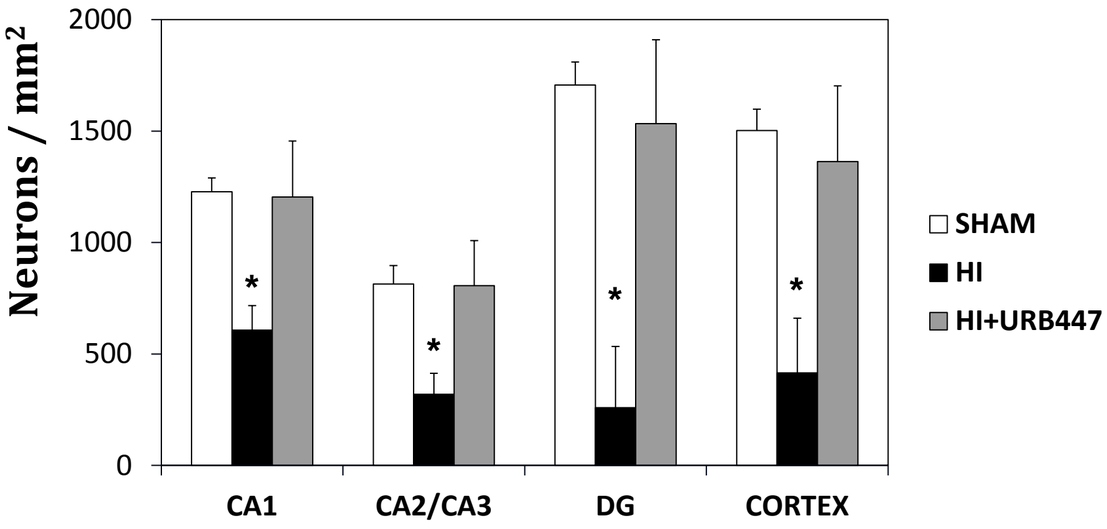


Figure 3. Neuronal density Nissl staining revealing extensive cell death after HI and maintenance after URB447 administration.

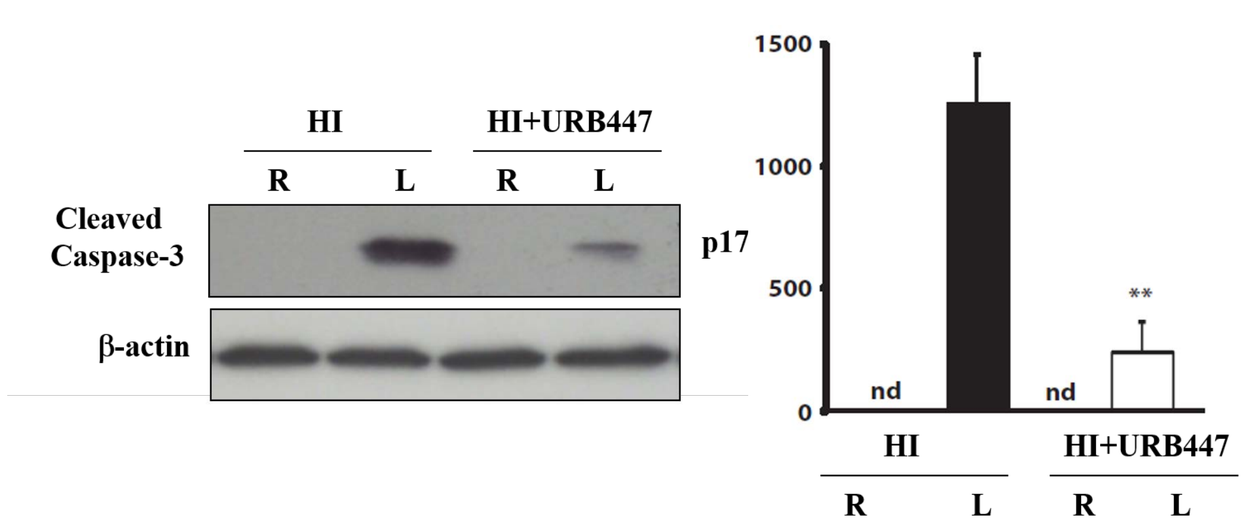


Figure 4. Caspase-3 activation induced by neonatal HI is blocked after URB447 treatment

Conclusions

In both short-term biochemical and long-term histological analyses, URB447 treatment blocked delayed cell death in vivo after neonatal ischemic brain injury.

Acknowledgments

This work was funded by EITB Maratoia-BIOEF (BIO18/IC/003) and the Spanish Ministry of Science and Innovation (MINECOR20/P66/AEI/10.13039/501100011033).