

## ENDOCANNABINOIDS CONTRIBUTE TO THE NEUROPROTECTIVE EFFECTS OF mGlu1 RECEPTOR ANTAGONISTS AGAINST POST-ISCHEMIC NEURONAL DEATH

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We have previously shown that antagonists of mGlu1 but not mGlu5 metabotropic glutamate receptors attenuate CA1 neuronal death in *in vivo* and *in vitro* models of cerebral ischemia by means of a mechanism that involves the release of GABA and activation of GABA receptors (1). Stimulation of mGlu1 postsynaptic receptors in CA1 pyramidal cells is known to promote the release of endogenous cannabinoids (2), that may act as retrograde transmitters to suppress the release of GABA following activation of CB1 receptors located on the presynaptic terminals of interneurons (3). In the present study, we examined whether agents acting on the endocannabinoid receptor CB1 could play a role in the mechanisms of mGlu1-mediated neuroprotection. We used organotypic rat hippocampal slices exposed to 30 min oxygen-glucose deprivation (OGD), which promotes CA1 injury 24 h later. When present in the incubation medium, the CB1 receptor agonists WIN 55212-2 (30-100  $\mu$ M) and CP-55940 (1-50  $\mu$ M) dose-dependently exacerbated CA1 injury induced by a 20 min, sublethal period of OGD. Conversely, incubation with the CB1 receptor antagonist AM 251 (0.1-1  $\mu$ M) significantly attenuated the selective CA1 damage induced by 30 min OGD. The CB1 receptor agonist WIN 55212-2, but not AM 251, significantly reverted the neuroprotective effects of the mGlu1 receptor antagonist LY367385 (100-300  $\mu$ M) and 3-MATIDA (100-300  $\mu$ M) in the more severe model (30 min OGD). The mGlu1/5 agonist DHPG (100  $\mu$ M) exacerbated CA1 injury induced by 20 min OGD, but this effect was not synergic with that of WIN 55212-2 (50  $\mu$ M). AM 251 (1  $\mu$ M), but not WIN 55212-2, was able to revert the neurotoxic effects of the mGlu1 agonist DHPG. Finally, WIN 55212-2 reduced the increase in the hippocampal output of GABA evoked by LY367385 in freely moving gerbils both under basal and ischemic conditions. Our results suggest that in the hippocampal CA1 the release of GABA contributes to the attenuation of OGD injury induced by mGlu1 receptor antagonists and that endocannabinoid receptors are involved in mediating the GABAergic effects of mGlu1 receptors.

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2) Varma N., Carlson G.C., Ledent C. & Alger B.E. (2001) J. Neurosci. 21: RC188

3) Chevaleyre V. & Castillo P.E. (2003) Neuron 38: 461-472