Neuroprotective effects of *N*-oleoylglycine in a mouse model of mild traumatic brain injury

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Traumatic brain injury (TBI) is the leading cause of death in the young age group and the most commonly identified cause of epilepsy in adult populations older than 35 years. At present, there are no effective drugs to treat brain injury (see Mechoulam and Shohami, *Mol. Neurobiol*. 2007 for review). Common neurological complications after TBI include pain, spasticity, and late functional decline. Pain may be acute or chronic. Interestingly, the brain injury literature describes the 'mild' or 'minor' traumatic brain injury group as reporting the most pain complaints. The role of the endocannabinoid system in neuroprotection is well established. Several groups reported enhanced levels of the endocannabinoid anandamide (AEA) after acute injury, and in response to TBI there is local and transient accumulation of the other endogenous agonist of cannabinoid receptors, 2-arachidonoylglycerol (2-AG) at the site of injury, peaking at 4 h and sustained up to at least 24 h (see Shohami et al., *Br. J. Pharmacol.* 2011 for review). Moreover, studies from Cohen-Yeshurun (*J. Cereb. Blood Flow Metab.*, 2011) and Mann and co-workers, (*J Neuroimmune Pharmacol.,* 2015) reported the role of N-arachidonoyl-L-serine (N-AA-Ser) and palmitoyl serine as new neuroprotective lipid mediators after TBI, thus raising the opportunity to investigate also the levels of these compounds and other endocannabinoid-like molecules in brain areas involved in TBI and their possible mechanism of action. The aim of this study was, therefore, to investigate the alterations of endocannabinoid levels in a model of mouse mild-TBI and to test the anti-hyperalgesic and neuroprotective effects of a poorly understood endogenous endocannabinoid-like compound, *N*-oleoyl-glycine (OlGly), in this model.

Mice underwent TBI using the weight drop model and were divided into seven experimental groups: naïve, sham, sham+OlGly 50 and 100 mg/kg, TBI, TBI+OlGly 50 and 100 mg/kg. Animals were treated with OlGly (i.p.) for 14 days once a day, starting one day after injury and underwent, several behavioural tests to assess pain and depression. At the end of the treatment, the animals were decapitated and brains were dissected for endocannabinoid analysis. Interestingly, treatment with OlGly normalized motor impairment and reckless behavior; reduced thermal hyperalgesia and mechanical allodynia and, moreover, normalized aggressiveness and depression induced by TBI. On the other hand, the levels of endocannabinoids did not undergo any change 65 days after TBI.
In conclusion, we found significant ameliorations in mice treated with OlGly, and the hypothesis that this compound, like *N*-arachidonoylglycine (Kohno et al., Biochem. Biophys. Res. Commun., 2006), might be an endogenous ligand for the orphan receptor GPR18 and, therefore, might exert neuroprotective and analgesic effects through this target, is currently under investigation.

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