Dimethyl fumarate attenuates neuroinflammation and neurobehavioral deficits induced by experimental traumatic brain injury.


University of Messina

TBI is a serious neuropathology that causes secondary injury mechanisms, including dynamic interplay between ischemic, inflammatory and cytotoxic processes. Moreover, the damage induces massive cell death and outcomes in extensive dendrite degeneration leading to persistent cognitive, sensory and motor dysfunction and resulting in a permanent neurobiological alteration. Fumaric acid esters (FAEs) showed beneficial effects in preclinical models of neuroinflammation, neurodegeneration and toxic oxidative stress, so the aim of the present work was to evaluate the potential beneficial effects of dimethyl fumarate (DMF), the most pharmacologically effective molecules among the FAEs, in a murine model of TBI induced by controlled cortical impact (CCI). Mice were orally administered with DMF at the doses of 1, 10 and 30 mg/Kg, 1h and 4h after CCI. DMF treatment notably reduced histological damage and improved behavioral function, observed by Rotarod and Elevated Plus Maze (EPM) tests. Moreover, DMF treatment was able to reduce edema and brain infarctions as evidenced by decreased 2,3,5-triphenyltetrazolium chloride staining (TTC) and a blocked apoptosis process increasing B-cell lymphoma 2 (Bcl-2) expression in the injured cortex. Furthermore, DMF treatment up-regulated Nrf-2 pathway, inducing activation of manganese superoxide dismutase (Mn-SOD) and heme-oxygenase-1 (HO-1). Also, regulating NF-κB pathway, DMF treatment decreased the severity of inflammation through a modulation of neuronal nitrite oxide synthase (nNOS), interleukin 1 (IL-1β), tumor necrosis factor (TNF-α) and ionized calcium-binding adapter molecule 1 (Iba-1) expression, and cyclooxygenase 2 (COX-2) and myeloperoxidase (MPO) activity. Our results showed important protective effects of DMF in an animal model of TBI, sustaining the thesis that DMF could provide a valuable support to the therapies for brain trauma available today.