DIMETHYL FUMARATE PROTECTS THE CNS AGAINST EXCITOTOXICITY

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BACKGROUND: Dimethyl fumarate (DMF), a novel oral treatment for multiple sclerosis (MS), has been shown to significantly reduce gadoliniumenhancing lesions and disease progression in relapsing-remitting MS (RRMS) in two recent phase 3 clinical trials. However, the possible neuroprotective function of DMF has not been fully investigated. **OBJECTIVES:** Our preliminary data suggest that DMF up-regulates heme oxygenase-1 (HO-1), an anti-oxidative and anti-inflammatory enzyme in the CNS. Interestingly, previous studies showed that overexpression of HO-1 in neurons protects neurons against toxicity caused by H2O2 and MPP. Based on these findings, our hypothesis is that DMF exerts its neuroprotective effects in MS through HO-1 induction.

METHODS:

In the current study, an excitotoxic animal model was induced by AMPA microinjection into the spinal cord at lumbar section. To evaluate DMF's neuroprotective effect, DMF was fed to naive mice for 3 days followed by AMPA microinjection. Neuronal death and behavior performance were evaluated 24 hours after injection. To determine whether HO-1 expression is altered, DMF was fed to naive mice for 3 days, and then HO-1 mRNA and protein expression in the brain and spinal cord were determined by PCR and ELISA, respectively.

RESULTS:

Our results demonstrate that DMF pretreatment reduces neuronal damage by 30% and improves behavioral outcomes as compared to vehicle-treated mice, indicating the neuroprotective effects of DMF. Additionally, both HO-1 mRNA and protein expression were significantly up-regulated in the spinal cord in the DMF-feeding mice compared to vehicle-treated mice, suggesting HO-1 as a potential target of DMF.

CONCLUSION:

Our data demonstrate that DMF protects the spinal cord against excitotoxicity, possibly through up-regulation of HO-1 in the CNS.

Supported by: National Multiple Sclerosis Society (NMSS 4358-A-13)
Disclosure: Nothing to disclose
Note: This abstract is under the Whitaker Research Track category.