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Effect of dimethyl fumarate on Apoptosis and Neuroinflammation in PTZ kindling model in rats

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Roles of apoptosis and neuroinflammation have been well established in the pathogenesis of epilepsy. It has been reported that the activation of nuclear factor-erythroid 2-related factor-2 (Nrf2) contributes to the attenuation of inflammation by inhibiting nuclear factor-kB (NF-kB) pathway. Current study was designed to evaluate anti-apoptotic, anti-inflammatory and anti-oxidative roles of dimethyl fumarate (DMF), an activator of Nrf2, in chemical kindling model in rats. Chemical kindling model was established in Wistar rats by intraperitoneal (i.p.) administration of pentylenetetrazole (PTZ). Animals were treated with DMF (60 mg/kg) to activate the Nrf2 antioxidant response element (ARE) pathway. The animals were assessed for seizure score, neuronal damage and inflammatory cytokines levels (IL-1β, IL-6 and TNF-α) in hippocampus. The mRNA levels of various genes (Nrf2, HO-1, NQO1, Bcl2, Bax, Caspase 3, NF-kB, IL-6, IL-1β and TNF-α) were quantified by real-time PCR. The expression of anti-oxidative (Nrf2), apoptotic (Bax, Bcl2) and inflammatory (NF-kB) proteins were analysed by western blot. Immunohistochemistry (Bax) and electron microscopy were done to assess apoptosis. There was reduction in the seizure score, percentage of kindled rats and neurological damage score in DMF treated rats. The levels of pro-inflammatory cytokines were also decreased by DMF treatment. DMF downregulated the expression of inflammatory (NF-kB) and apoptotic (Bax, Caspase-3) genes and proteins. DMF treatment increased the gene expression of Nrf2, HO-1, NQO1, Bcl-2 and protein expression of Nrf2 and Bcl2. The present study demonstrated anti-apoptotic, anti-inflammatory and anti-oxidative effect of DMF in PTZ kindled rats. Therefore, it could be a potential new avenue to target the pathological changes during epileptogenesis.

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