World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:19, No:03, 2025

Dimethyl fumarate Alleviates Valproic Acid-Induced Autism in Wistar Rats via Activating NRF-2 and Inhibiting NF-κB Pathways

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Abstract : Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social deficits and repetitive behavior. Multiple studies suggest that oxidative stress and neuroinflammation are key factors in the etiology of ASD and often associated with worsening of ASD-related behaviors. Nuclear factor erythroid 2-related factor 2 (NRF-2) is a transcription factor that promotes expression of antioxidant response element genes in oxidative stress. In ASD subjects, decreased expression of NRF-2 in frontal cortex shifted the redox homeostasis towards oxidative stress, and resulted in inflammation evidenced by elevation of nuclear factor kappa B (NF-κB) transcriptional activity. Dimethyl fumarate (DMF) is a NRF-2 activator that is used in the treatment of psoriasis and multiple sclerosis. It participates in the transcriptional control of inflammatory factors via inhibition of NF-κB and its downstream targets. This study aimed to investigate the role of DMF in alleviating the cognitive impairments and behavior deficits associated with ASD through mitigation of oxidative stress and inflammation in prenatal valproic acid (VPA) rat model of autism. Methods: Pregnant female Wistar rats received a single intraperitoneal injection of VPA (600 mg/kg) to induce autistic-like-behavioral and neurobiological alterations in their offspring. Chronic oral gavage of DMF (150mg/kg/day) started from postnatal day (PND) 24 till PND62 (39 days). Prenatal VPA exposure elicited autistic behaviors including decreased social interaction and stereotyped behavior. Social interaction was evaluated using three-chamber sociability test and calculation of sociability index (SI), while stereotyped repetitive behavior and anxiety associated with ASD were assessed using marble burying test (MBT). Biochemical analyses were done on prefrontal cortex homogenates including NRF-2, and NF-κB expression. Moreover, inducible nitric oxide synthase (iNOS) gene expression and tumor necrosis factor (TNF-□) protein expression were evaluated as markers of inflammation. Results: Prenatal VPA elicited decreased social interaction shown by decreased SI compared to control group ($p < 0.001$) and DMF enhanced SI ($p < 0.05$). In MBT, prenatal injection of VPA manifested stereotyped behavior and enhanced number of buried marbles compared to control ($p < 0.05$) and DMF reduced the anxiety-related behavior in rats exhibiting ASD-like behaviors ($p < 0.05$). In prefrontal cortex, NRF-2 expression was downregulated in prenatal VPA model ($p < 0.0001$) and DMF reversed this effect ($p < 0.0001$). The inflammatory transcription factor NF-κB was elevated in prenatal VPA model ($p < 0.0001$) and reduced ($p < 0.0001$) upon NRF-2 activation by DMF. Prenatal VPA expressed higher levels of proinflammatory cytokine TNF-□ compared to control group ($p < 0.0001$) and DMF reduced it ($p < 0.0001$). Finally, the gene expression of iNOS was downregulated upon NRF-2 activation by DMF ($p < 0.01$). Conclusion: This study proposes that DMF is a potential agent that can be used to ameliorate autistic-like-changes through NRF-2 activation along with NF-κB downregulation and therefore, it is a promising novel therapy for ASD.

Keywords : autism spectrum disorders, dimethyl fumarate, neuroinflammation, NRF-2
Conference Title : ICPP 2025 : International Conference on Pharmacy and Pharmacology
Conference Location : Doha, Qatar
Conference Dates : March 25-26, 2025