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Combined use of magnesium sulphate and fingolimod for antenatal neuroprotection against inflammation-mediated preterm brain injury

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Objective

Fingolimod (fng) is a disease-modifying agent used in multiple sclerosis treatment with neuroprotective and anti-inflammatory effects. Our recent research showed foetal neuroprotective effects of antenatal fng treatment in the rat model. Here, we aim to expand our knowledge on antenatal fng therapy in comparison to standard neuroprotection with magnesium sulphate (Mg-sulphate). We also hypothesized that combined treatment (fng plus Mg-sulphate) is more effective than single-agent prophylaxis against foetal brain injury.

Methods

Twenty-eight pregnant rats were evaluated in 7 experimental groups at 0. 80 gestation: (1) intraperitoneal (IP) saline only, (2) IP endotoxin only, (3) IP endotoxin + subcutaneous Mg-sulphate (270 mg/kg loading dose followed by 27 mg/kg maintenance every 20 minutes until delivery), (4) IP endotoxin + IP fng (4 mg/kg), (5) IP endotoxin + Mg-sulphate + fng, (6) saline + fng, and (7) saline + Mg-sulphate + fng. Preterm delivery was induced by hysterotomy 6 h after endotoxin administration, and foetal brain samples were evaluated for interleukin-6 (IL-6), interleukin-10 (IL-10), and S100 beta by immunohistochemistry.

Results

The validation of the experimental model was confirmed by increased IL-6, reflex increase in IL-10, and increased S100 beta staining in endotoxin-exposed animals compared to vehicle controls. Both magnesium and fng decreased IL-6, IL-10, and S100 beta staining in endotoxin-exposed animals ($p<0.01$ for all comparisons). Fng was more effective in mitigating IL-6 expression compared to Mg-sulphate ($p=0.01$). Combined treatment was associated with decreased IL-10 ($p=0.001$) and IL-6 ($p=0.001$) staining compared to Mg-sulphate alone. Fng or combined fng + Mg-sulphate did not have any detrimental effects in non-endotoxin-exposed pups' brain tissues.

Conclusion

Fng is an attractive novel candidate drug against inflammation-induced preterm brain injury and seems to have an additive effect when combined with Mg-sulphate treatment. Supported by grants from Suleyman Demirel University Scientific Research Projects Coordination Unit (research project no, 4942-TU2-17).