Modulation of Inflammatory Signaling and Cytokine Release from Microglia by Celastrol Incorporated into Dendrimer Nanocarriers

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Abstract:

Aim: This study investigates the capacity of a potent anti-inflammatory nanomedicine, celastrol, incorporated into poly(amidoamine) dendrimers, to inhibit endotoxin-mediated signaling in microglia. Materials & methods: Celastrol was incorporated into amino (Cel/G4-NH2) and hydroxyl (Cel/G4-OH) terminus poly(amidoamine) (G4) dendrimers. Cell viability, release of nitric oxide, IL-6, TNF-□ and activation of MAPK (e.g., p38 and JNK) and NF-□B were assessed in endotoxin (i.e., lipopolysaccharide) stimulated microglial cells. Results: G4-OH and G4-NH2 increased celastrol aqueous solubility by seven- and 12-fold, respectively. G4-OH and Cel/G4-OH suppressed lipopolysaccharide-mediated release of proinflammatory mediators, such as nitric oxide and IL-6, but not TNF-□, without reducing microglial cell viability, while Cel/G4-NH2 potentiated cytotoxicity and cytokine release. Blockade of proinflammatory signaling was accompanied by attenuation of p38 MAPK activation. Conclusion: This study supports the potential use of poly(amidoamine) dendrimers for effective anti-inflammatory therapy in the chronically inflamed CNS.

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