The Modulatory Role of 2-Methoxyestradiol in M1/M2 Polarization of Glial Cells

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ABSTRACT

Activation of the M1 microglial phenotype plays a key role in the progression of central nervous system (CNS) disorders and is a significant contributor to neuroinflammatory diseases. Contrariwise, M2 macrophages exhibit anti-inflammatory activities that promote tissue repair and reduce inflammation in the CNS. Thus, converting pro-inflammatory M1 to the anti-inflammatory M2 has emerged as a potential therapeutic approach to prevent the progression of neuroinflammatory diseases. 2-Methoxyestradiol (2-ME), a metabolite of estradiol, has gained interest for its remarkable anti-inflammatory properties. This study aimed to evaluate the modulatory effects of 2-ME on M1 polarisation in lipopolysaccharide (LPS) stimulated-IMG microglial cells. Firstly, the cells were treated with different concentrations of 2-ME to assess its cytotoxicity. Then, the modulatory effects of 2-ME on inflammatory markers were evaluated. Quantitative PCR (qPCR) was conducted to measure mRNA expression levels of IL-6, IL-1β, TNF-α, and TGF-β1. The protein concentrations of these cytokines were determined via enzyme-linked immunosorbent assays (ELISA). Additionally, flow cytometry was used to determine cell surface markers (CD86 and CD206) in IMG cells subjected to LPS or IL-4. The results revealed that 2-ME exhibited no cytotoxicity towards IMG cells. In addition, 2-ME significantly inhibited the upregulation of typical M1 markers including IL-6, IL-1β, and TNF-α both at the gene and protein levels. Flow cytometry analysis showed that 2-ME effectively decreased the expression of M1 marker (CD86) in LPS-stimulated IMG cells, while IL-4-stimulated cells treated with 2-ME displayed a marked increase in M2 marker (CD206) expression. In conclusion, 2-ME plays a modulatory role in microglial polarization, enhances the shift towards the M2 phenotype, and emphasizes its potential therapeutic value in the treatment of neuroinflammatory disorders.

Keywords: 2-Methoxyestradiol; Macrophages; Microglia; Lipopolysaccharides

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