Methylprednisolone inhibits the expression of glial fibrillary acidic protein and chondroitin sulfate proteoglycans in reactivated astrocytes

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摘要

創傷後的神經膠質增生導致硫酸軟骨素蛋白聚糖(CSPG)的顯著表達,從而抑制軸突生長和再生.甲基強地松龍(MP),一種合成的糖皮質激素,在急性脊髓損傷(SCI)的治療中有神經保護作用和抗炎效應.但是,MP 對於 CSPG 在活性膠質細胞中的表達的作用尚不清楚.本文用 a-氨基-3-羥基-5-甲基-4-異惡唑丙酸酯(AM-PA)誘導星形膠質細胞再活化,用環噻嗪模擬 SCI 的興奮性中毒刺激.AMPA 治療後,星形膠質細胞再活化的標誌物-膠質纖維酸性蛋白(GFAP)、CSPG 神經聚糖和磷酸鹽的表達都顯著上調.AMPA 治療星形膠質細胞的條件培養液強烈抑制大鼠背根神經節中神經元的軸突生長,但這種作用能被 MP 的預處理所逆轉.此外,MP 下調成年 SCI 大鼠中 GFAP 和 CSPG 的表達,對抗 RU486 的糖皮質激素受體(GR)和 GR siRNA 能逆轉 MP 對 GFAP 和神經聚糖表達的抑制作用.這些結果提示,MP 能在興奮性中毒損傷後通過 GR 介導的星形膠質細胞再活化下調和 GSPG 表達抑制來改善神經修復,促進軸突生長.

Abstract

Reactive gliosis caused by post-traumatic injury often results in marked expression of chondroitin sulfate proteoglycan (CSPG), which inhibits neurite outgrowth and regeneration. Methylprednisolone (MP), a synthetic glucocorticoid, has been shown to have neuroprotective and anti-inflammatory effects for the treatment of acute spinal cord injury (SCI). However, the effect of MP on CSPG expression in reactive glial cells remains unclear. In our study, we induced astrocyte reactivation using -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and cyclothiazide to mimic the excitotoxic stimuli of SCI. The expression of glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivation, and CSPG neurocan and phosphacan were significantly

elevated by AMPA treatment. The conditioned media from AMPA-treated astrocytes strongly inhibited neurite outgrowth of rat dorsal root ganglion neurons, and this effect was reversed by pretreatment with MP. Furthermore, MP downregulated GFAP and CSPG expression in adult rats with SCI. Additionally, both the glucocorticoid receptor (GR) antagonist RU486 and GR siRNA reversed the inhibitory effects of MP on GFAP and neurocan expression. Taken together, these results suggest that MP may improve neuronal repair and promote neurite outgrowth after excitotoxic insult via GR-mediated downregulation of astrocyte reactivation and inhibition of CSPG expression.