Nuclear Factor-kappa B 在過度醣化最終產物誘導 RAW 264.7 巨噬細胞表現一氧化氮合成酶;中所扮演的角色

Involvement of Nuclear Factor-kappa B in Advanced Glycosylation End Products-Induced Inducible Nitric Oxide Synthase Expression in RAW 264.7 Macrophages

中文摘要

過度醣化最終產物(Advanced glycosylation end products, AGEs)已被證實與糖尿病併發症的病理有關。本篇論文主要是探討在 RAW 264.7 巨噬細胞中，過度醣化最終產物在誘導型一氧化氮合成酶(inducible nitric oxide synthase, iNOS)表現的影響。利用過度醣化最終產物處理 RAW 264.7 巨噬細胞後，一氧化氮的產生和誘導型一氧化氮合成酶的表現會以劑量及時間相關性增加。Nuclear factor-kappa B (NF-kB)之抑制劑 pyrrolidone dithiocarbamate (PDTC)會抑制過度醣化最終產物所引起一氧化氮的產生和誘導型一氧化氮合成酶的表現。若以過度醣化最終產物處理 RAW 264.7 巨噬細胞 30 分鐘會引起 NF-kB 由細胞質轉位到細胞核內。在 electrophoretic mobility shift assay (EMSA)的結果中，過度醣化最終產物也會增加 NF-kB 結合基因的能力。而 Tyrosine kinase 之抑制劑 genistein、phosphatidylinositol-3-kinase (PI-3K)之抑制劑 LY 294002、phosphatidylcholine-phospholipase C (PC-PLC)之抑制劑 D 609、protein kinase C (PKC)之抑制劑 Ro 31-8220 和 p38 mitogen-activated protein kinase (MAPK)之抑制劑 SB 203580 會抑制過度醣化最終產物所引起一氧化氮的產生和誘導型一氧化氮合成酶的表現，表示 tyrosine kinase、PI-3K、PC-PLC、PKC、p38 MAPK 和 NF-kB 參與此訊號傳遞路徑中。而 NF-kB 的轉位和結合基因的能力也會被 genistein、LY 294002、D 609、Ro 31-8220 和 SB 203580 所抑制。綜合以上的結果可知過度醣化最終產物刺激 RAW 264.7 巨噬細胞的一氧化氮產生和誘導型一氧化氮合成酶表現是經由 NF-kB 的活化，而活化 NF-kB 的上游訊號傳遞路徑可能有 tyrosine kinase、PI-3K、PC-PLC、PKC、p38 MAPK 的參與。

英文摘要

Advanced glycosylation end products (AGEs) have been implicated in the pathogenesis of diabetic complications. In this study, the effect of AGEs on inducible nitric oxide synthase (iNOS) expression in RAW 264.7 macrophages has been investigated. Treatment of RAW 264.7 macrophages with AGEs caused a dose- and time-dependent increase of nitric oxide (NO) production and iNOS expression. Treatment of RAW 264.7 macrophages with AGEs for 30 min stimulated the translocation of NF-kB from cytosol to nucleus. Electrophoretic mobility shift assay revealed that the NF-kB DNA-protein binding activity was enhanced by AGEs. AGEs-induced NO production and iNOS expression were blocked by the tyrosine kinase inhibitor, genistein, the phosphatidylinositol-3-kinase (PI-3K) inhibitor, LY 294002, the phosphatidylcholine-phospholipase C (PC-PLC) inhibitor, D 609, the protein kinase C (PKC) inhibitor, Ro 31-8220, the p38 mitogen-activated protein kinase (MAPK) inhibitor, SB 203580, and the nuclear factor-kappa B (NF-kB) inhibitor, pyrrolidone dithiocarbamate (PDTC), suggesting that tyrosine kinase, PI-3K, PC-PLC, PKC, p38 MAPK and NF-kB are involved in this signaling event. AGEs-stimulated translocation and DNA binding activity of NF-kB were inhibited by genistein, LY 294002, D 609, Ro 31-8820, SB 203580 and PDTC. In conclusion, AGEs might activate NF-kB via an upstream signaling cascade which composed of tyrosine kinase, PI-3K, PC-PLC, PKC, and p38 MAPK, resulting the induction of iNOS protein expression and NO release in RAW 264.7 macrophages.