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• 計畫英文名稱	Advanced Glycosylation End Products-Induce Nitric Oxide Synthase Expression in C6 Glioma Cells: Involvement of P38 MAP Kinase Dependent Mechanism
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• 中文關鍵字	高度糖化終產物；一氧化氮合成？；MAP 激？；神經膠瘤細胞
• 英文關鍵字	Advanced glycosylation end product；Nitric oxide synthase；MAP kinase；Glioma cell
• 中文摘要	在許多退行性神經病變及阿滋海默症中,誘導型一氧化氮合成？(iNOS)的活性扮演著重要的角色。而過度糖化的最終產物(AGEs)已被證實和在阿滋海默症的類澱粉斑形成有關。本研究主要在探討 AGEs 是否可以誘發一氧化氮合成的表現,及其蛋白表現調控的訊息傳遞路徑。我們發現在 C6 神經膠瘤細胞中 AGEs 可以增加 Nitrite 的產生及 iNOS 的表現。在 C6 神經膠瘤細胞中,隨著 AGEs 劑量的增加或是反應時間的增加,Nitrite 的產生都會隨之增加。AGEs 誘導產生的一氧化氮,可以被 Actinomycin D、Cycloheximide 以及一氧化氮合成？抑制劑 1-NAME 所抑制。預先以抗 AGEs 抗體(1:100)處理 C6 神經膠瘤細胞,也可將由 AGEs 刺激所產生的 NO 抑制下來,另一方面,預先以 Genestein 或 FPT-II 抑制劑,或 SB203580 處理 C6 神經膠瘤細胞,發現對於 AGEs 誘導產生的 Nitrite 有抑制作用。AGEs 可以活化 P38 MAP kinase,同時此反應可以被 Genestein(20.mu.M)、FPT-II 抑制劑(20.mu.M)以及 SB203580(10.mu.M)所抑制。綜合以上所述,我們的實驗結果顯示,在 C6 神經膠瘤細胞中,AGEs 誘發 iNOS 蛋白表現以及 NO 產生的訊息傳遞路徑,P38 MAP Kinase 也包含在其中。
• 英文摘要	Induction of iNOS is important in amyloid plagues formation. Given accumulation of AGEs in the brain is linked to Alzheimer's disease, we investigated whether iNOS protein expression is induced by AGEs and whether Ras-MAPK pathway is involved in the AGEs-induced iNOS expression in C6 glioma cells. AGEs caused a dose- and time-dependent increase of nitrite accumulation in C6 glioma cells. The AGEs-stimulated NO production from C6 glioma cells was inhibited by actinomycin D, by cycloheximide and by

the NO synthase inhibitor, 1-NAME, suggesting the increase of AGEs-induced nitrite release is due to iNOS up-regulation. Consistently, treatment of C6 glioma cells with AGEs stimulated the inducible nitric oxide synthase (iNOS) protein expression. AGEs-stimulated NO production was inhibited by pretreatment of C6 glioma cells with anti-AGEs antibodies (1:100). Pretreatment with genestein (the protein tyrosine kinase inhibitor), or FPT II inhibitor (the Ras-farnesyl transferase inhibitor), or SB203580 (the p38 MAPK inhibitor), prior to the AGEs addition to C6 glioma cells results in partial suppression of AGEs-induced iNOS expression and nitrite release from C6 glioma cells. AGEs activate p38 MAP kinase in C6 glioma cells and the effect was blocked by genesteine (20.mu.M), FPT-II inhibitor (20.mu.M) and SB203580 (10.mu.M). Taken together, our data suggest that p38 MAP kinase is involved in AGEs induced iNOS expression and NO production in C6 glioma cells.