Tanshinone IIA 經由 Phosphatidylinositol 3-kinase /Akt 路徑誘導血紅素氧化酵素-1 而抑制脂多醣體所誘導的一氧化氮與環氧酵素-2 的表現

Tanshinone Induces Heme Oxygenase-1 Expression through Phosphatidylinositol 3-kinase /Akt Pathway and Suppresses Lipopolysaccharide-Induced Inducible Nitric Oxide and Cyclooxygenase-2 Expression in Raw264.7 Cells.

中文摘要

在中國丹蔘（Danshen, Salvia miltiorrhiza Bunge, Radix Salvia）被廣泛的使用於治療發炎症狀以及心臟疾病。Tanshinone IIA 是從丹蔘中所純化出來的一種雙?類成分。Tanshinone IIA 具有抗發炎效果以及影響粒線體電子傳遞鏈中電子的傳遞。本研究利用 Raw 264.7 cells 發現 tanshinone IIA 能夠增加 Raw 264.7 cells 中活性氧自由基（reactive oxygen species；ROS）的含量，進而誘導血紅素氧化酵素-1（heme oxygenase-1；HO-1）的蛋白表現。使用 PI 3-K 抑制劑（LY294002）和 ERK 抑制劑（PD98059）可以有效抑制 tanshinone IIA 誘導的 HO-1 蛋白表現。以 tanshinone IIA 處理 Raw 264.7 cells，再以酯多醣（lipopolysaccharide；LPS）刺激細胞後，tanshinone IIA 可以有效抑制 LPS 所誘導的誘導型一氧化氮合成酵素 （inducible Nitric Oxide Synthese；iNOS ）和環氧酵素-2（cyclooxygenase-2；COX-2）的表現。接下來利用 HO-1 競爭型抑制劑（tin protoporphyrin；SnPP）和 CO 清除劑（hemoglobin；Hb）都能有效阻斷 tanshinone IIA 抑制 LPS 所誘導的一氧化氮（nitric oxide；NO）之產生。另外 tanshinone IIA 可以有效抑制 LPS 所誘導的磷酸化 I　B。因此，tanshinone IIA 可能透過活化 PI 3-K/Akt 以及 ERK 訊息傳導路徑，誘導細胞中 HO-1 的表現，並經由 HO-1 的下游產物 CO 抑制由 LPS 所誘導的 iNOS 的表現。

英文摘要

Tanshinone IIA, an active ingredient purified from the Chinese herb Danshen（Salvia miltiorrhiza Bunge, Radix Salvia）, exerts anti-inflammatory effects and influences electron transfer reaction in mitochondria. In the present study, we demonstrated that tanshinone IIA inhibited LPS-induced iNOS and COX-2 expression in Raw 264.7 cells. Incubation of Raw 264.7 cells with tanshinone IIA increased heme oxygenase-1 (HO-1) expression, which was inhibited by pretreatment of cells with l-N-acetylcysteine (l-Nac) prior to addition of tanshinone IIA. In the contrast, pretreatment of cells with l-buthionine-(S, R)-sulfoximine (BSO) reduced tanshinone

IIA-induced HO-1 expression, suggesting that reactive oxygen species (ROS) were involved. Treatment cells with tanshinone IIA also increasd intracellular reactive oxygen species (ROS). Using PI 3-K inhibitor (LY294002) and ERK inhibitor (PD98059) attenuated tanshinone IIA-induced Heme oxygenase-1 expression. In agreement, incubation of cells with tanshinone IIA increased phosphorylation of Akt and ERK. The inhibition of LPS-stimulated iNOS expression and NO production by tanshinone IIA was reversed by tin protoporphyrin (SnPP), suggesting tanshinone IIA might exert this inhibitory effect through HO-1. Addition of CO donor mimicked the tanshinone IIA effect on suppressing LPS-induced inducible nitrite oxygen synthease (iNOS) and COX-2 expression. Scavenging of CO by hemoglobin significantly reversed the inhibition of LPS-stimulated nitrite accumulation by tanshinone IIA. In addition, treatment cells with tanshinone IIA reducd LPS-stimulated I B phosphorylation. Taken together, these results suggest that tanshinone IIA exerts its inhibitory effect through induction of HO-1 expression. HO-1 catalyzes the formation of CO, which in turn inhibit iNOS induction.