磷酸二酯?亞型三選擇性抑制劑木質素黃酮加強亞型四抑制劑橙皮素的抗氣喘作用

Anti-asthmatic effects of hesperetin, a selective phosphodiesterase (PDE)4 inhibitor, potentiated by daidzein, a selective PDE3 inhibitor

中文摘要

磷酸二酯?亞型四選擇性抑制制 (PDE4 inhibitors) 會使 cAMP 增加，因此有氣管的舒張及抗發炎的作用，是未來治療氣喘值得發展的藥物。而磷酸二酯?亞型三選擇性抑制制 (PDE3 inhibitors) 也會使 cAMP 增加，當二者合併使用是否有加成或加強 PDE4 inhibitors 的效果，是本研究的主要目標。

橙皮素 (hesperetin, PDE4 inhibitor) 在 100 μM 時可以使卵蛋白敏感化之天竺鼠氣管基本張力鬆弛，而合併木質素黃酮 (daidzein, PDE3 inhibitor) 100 μM 則有加成抑制效果。另外，當兩者各 100 μM 合併使用會鬆弛 histamine (30 μM) 引起的預先收縮達 aminophylline (1 mM) 最大鬆弛的 80.1 ± 3.3%，有意義地大於兩者 (300 μM) 單獨使用的效果。而 hesperetin (300 μM) 或 diadzein (300 μM) 不會取代一半結合在腦細胞顆粒 high affinity rolipram binding sites (HARBS) 之[3H]-rolipram，且兩者合併也不會增加和 HARBS 的結合能力。

目前選擇性 PDE4 inhibitors 各國藥廠爭先發展，但受限於噁心、嘔吐和胃酸過度分泌等副作用而難突破，在二次過敏原激釁 BALB/c 小白鼠的氣喘模式下，雖然 daidzein (1 μmol/kg, i.p.) 與 hesperetin (10 μmol/kg, i.p.)，但非單獨使用，能有意義地抑制氣道過度反應，甚至有加強作用，與對照組相較，能使 methacholine (MCh, 50 mg/ml) 引起的 Penh 值下降，也同時可以有意義地使肺泡灌洗液 (BALF) 中的總發炎細胞、淋巴球、嗜中性白血球和嗜酸性白血球降低，以及減少 BALF 中之細胞激素 IL-5 和 TNF-α，此外對於血清中的 total IgE 及 BALF 中 OVA-specific IgE 也會有意義地下降。

兩者合併使用能抑制此種氣喘模式之氣道過度反應、使氣管舒張、有抗發炎的作用，同時也降低了可能的副作用，所以 daidzein 1 μmol/kg 與 hesperetin 10 μmol/kg 合併使用是最理想的搭配，因本研究結果顯示 daidzein 1 μmol/kg 與 hesperetin 3 或 30 μmol/kg 合併，抗氣喘效果都較差。

英文摘要

Selective PDE4 inhibitors increase cAMP level, therefore have bronchodilatory and anti-inflammatory effects, and is worth to develop for ameliorating asthma in the future. Selective PDE3 inhibitors also increase cAMP level. Whether addition or potentiation will be observed when they combine each other is the aim of the present study.

Hesperetin (PDE4 inhibitor) at 100 μM dilated baseline tension of ovalbumin (OVA)-sensitized guinea pig trachealis. When combined with 100 μM of diadzein (PDE3 inhibitor), addition was observed. In addition, the relaxant effect of combination of these two on histamine (30 μM)-induced precontraction in isolated non-sensitized guinea pig trachealis was 80.1 ± 3.3% of aminophylline (1 mM)-induced maximal relaxation, and significantly greater than that of either (300 μM) alone. However, hesperetin (300 μM) or diadzein (300 μM) did not displace a half of [3H]-rolipram binding from high affinity rolipram binding sites (HARBS) in brain particles. Combination of these two (300 μM, each) also did not increase the displacement ability from HARBS.

Many pharmaceutical manufactories of the world are trying to develop selective PDE4 inhibitors as anti-asthmatic drugs, nowadays, but the side effects, such as nausea, vomiting, gastric acid hypersecretion, induced by these drugs constrict their development. In the sensitized and OVA-secondarily challenged BALB/c mice, an asthmatic animal model, daidzein (1 μmol/kg, i.p.) significantly potentiated the lowering effect by hesperetin (10 μmol/kg, i.p.) when they combine each other, but not singly applied daidzein (1 μmol/kg, i.p.), on methacholine (MCh, 50 mg/ml)-induced enhanced pause (Penh) in control group. The combination also significantly reduced total cells, lymphocytes, neutrophils, eosinophils, IL-5, TNF-α and OVA-specific IgE in BALF. In addition, it also significantly decreased total IgE in serum.

The combination suppressed airway hyperresponsiveness (AHR) and had brochodilatory and anti-inflammatory effects with a benefit of decreasing side effects in the model of allergic asthma. The combination of daidzein (1 μmol/kg, i.p.) and hesperetin (10 μmol/kg, i.p.) seems the most appropriate, because other combination, such as daidzein (1 μmol/kg, i.p.) with hesperetin either at 3 or 30 μmol/kg (i.p.), only had less anti-asthmatic effects, in the present results