Quercetin-3,5,7,3',4'-O-pentamethylether 抑制卵蛋白－引起的氣道過度反應

Quercetin-3,5,7,3',4'-O-pentamethylether inhibits ovalbumin-induced airway hyperresponsiveness

中文摘要

Quercetin-3,5,7,3',4'-O-pentamethylether (QPME) 對 PDE1-4 抑制的 IC50 值< 10 μM，其 PDE4H/PDE4L 爲 11，與目前臨床試驗中最具潛力的抗氣喘藥 AWD 12-281 相同，本篇實驗將進一步探討 QPME 是否具有抗氣喘的功效。

在 vivo 方面，將 BALB/c 小白鼠腹腔內注射卵蛋白 (ovalbumin, OVA)，使其敏感化，再以卵蛋白氣化噴霧二次激釁 (secondary challenge) 後，利用整體體積描述器 (whole-body plethysmograph) 來分析因 methacholine (MCh, 6.25-50 mg/ml) 引起的氣道過度反應 (airway hyperresponsiveness response,AHR)，結果顯示 QPME (10~100 mol/kg, i.p.) 能劑量依存性地減少因 MCh (25~50 mg/ml) 噴霧而增加的 Penh 值，QPME (100 mol/kg) 亦能有意義地抑制因 MCh (25 mg/ml) 增加的 Penh 值，QPME (10-100 mol/kg) 也有意義地抑制肺泡灌流液 (BALF) 之總發炎細胞數、巨噬細胞、淋巴球、嗜中性白血球及嗜酸性白血球，並有意義地降低 IL-2、IL-4、IL-5、IFN-γ及 TNF- 的釋放，雖然有些例外，即最低劑量不能抑制總發炎細胞數、巨噬細胞、IL-5 及 IFN-γ的釋放。

在 vitro 方面，QPME (30~100 M) 能有意義地鬆弛基本張力及抑制 OVA (10~100 g/ml) 引起的敏感化天竺鼠氣管之收縮。

由 Lineweaver-Burk 分析發現 QPME (3~30 M) 對 PDE1、PDE2、PDE3 及 PDE4 呈現競爭性的抑制，所得 Ki 值分別爲 0.89, 1.07, 0.53 及 0.52 M，彼此間無意義差，顯示無特殊選擇性，可能由於無選擇性抑制 PDE1-4，而增加細胞內 cAMP，所以才有抗發炎及抗氣喘的功效。

英文摘要

Quercetin-3,5,7,3',4'-O-pentamethylether (QPME) inhibited activities of PDE1~4, with IC50 values < 10 M. The PDE4H/PDE4L ratio of QPME is about 11, equal to that of AWD 12-281 which is in clinical trial phase II. QPME whether possesses anti-asthmatic effect is the aim of this investigation.

In vivo, female BALB/c mice were sensitized by an intraperitoneal injection of ovalbumin (OVA), then challenged via the airway by ultrasonic nebulization of 1% OVA two periods (secondary challenge). After secondary challenge, the airway hyperresponsiveness (AHR) was measured in unrestrained animals, nebulized with methacholine (MCh, 6.25~50 mg/ml), by barometric plethysmography using a

whole-body plethysmograph. In the present results, QPME (10~100 mol/kg, i.p.) dose-dependently attenuated the enhanced pause (Penh) value induced by MCh (25~50 mg/ml). Furthermore, QPME (100 mol/kg, i.p.) also significantly inhibited MCh (25 mg/ml)-induced Penh value. QPME (10-100 mol/kg, i.p.) also significantly inhibited total inflammatory cells, macrophages, neutrophils , lymphocytes, and eosinophils in BALF after determination of Penh values. It also significantly attenuated the release of IL-2, IL-4, IL-5, IFN-γ, and TNF-α, with some exceptions that QPME at the least dose did not suppress releases of total inflammatory cells, macrophages, IL-5, and IFN-γ.

In vitro, QPME (30~100 M) significantly relaxed baseline tension and inhibited cumulative OVA (10~100 μg/ml)-induced contractions in isolated sensitized guinea pig trachealis.

According to the Lineweaver-Burk analysis, QPME (3~30 M) competitively inhibited PDE1, PDE2, PDE3, and PDE4 activities. The Ki values were 0.89, 1.07, 0.53, and 0.52 M which did not differ each other. Owing to QPME did not selectively inhibited PDE1-4, and resulted increase of intracellular cAMP, it may possess anti-inflammatory and anti-asthmatic effects.