# Quercetin methyl ether 衍生物在離體天竺鼠氣管的鬆弛作用與結構-活 性關係

# Relaxant effects of quercetin methyl ether derivatives in isolated guinea-pig trachea and their structure-activity relationships


## 中文摘要

我們分析 quercetin methylether 衍生物， 包括 quercetin 4'-methylether (tamarixetin)、quercetin 3,4',7-trimethyl ether (ayanin)、quercetin 3,3',4',7-tetramethylether (QTME) 及 quercetin 3,3',4',5,7-pentamethylether (QPME) 對氣管的鬆弛活性，並與我們以前有關 quercetin 和 quercetin 3-methylether 的研究比較，以瞭解它們的 structure-activity relationship (SAR)。上述 quercetin methylether 衍生物對 histamine (30 mM)、carbachol (0.2 mM) 及 KCl (30 mM) 預縮的離體天竺鼠氣管，產生劑量依存性的鬆弛作用，由其 IC25 得其活性大致依序爲 QPME、quercetin 3-methyl ether > quercetin、ayanin > tamarixetin > QTME， 其 SAR 如下: (a) Quercetin 的第 3 或第 5 位甲基化後，如 quercetin 變成 quercetin 3-methylether 或 QTME 變成 QPME，會使活性明顯上升；(b) quercetin 的第 3'或第 4'位甲基化後，如 ayanin 變成 QTME 或 quercetin 變成 tamarixetin，會使活性下降；(c) 甲基化的數目越多活性不一定越強，如 QTME 的鬆弛效果最差及 ayanin 的活性低於 quercetin 3-methylether 等。

上述 quercetin methylether 衍生物中較強的 QPME 預處理能非競爭性地對抗累加 histamine、carbachol 或 KCl 引起的收縮，其對 carbachol 及 KCl 的 pD2' 值有意義地小於它們的 -logIC50，顯示 QPME 抑制 carbachol 及 KCl 所引起的內鈣釋放小於抑制它們所引起的外鈣內流，而在對抗累加 histamine 所引起的收縮上則無此現像。在高鉀 (60 mM) 無鈣溶液中，QPME 也能非競爭性地抑制累加外鈣引起的收縮，並且對 histamine (30 mM) 預縮而 nifedipine (10 mM) 引起的最大鬆弛產生更進一步的鬆弛，表示除了能抑制 voltage (VOC) 及/或 receptor operated ccium channels (ROC) 外，尚有其他的鬆弛機轉。

然而其鬆弛反應不受上皮細胞去除或 propranolol (1 mM)、glibenclamide (10 mM)、methylene blue (25 mM) 及 2',5'-dideoxyadenosine (10 mM) 存在的影響，表示其鬆弛作用與 epithelium-derived relaxing factor(s)、b-adrenoceptor 受體活化、ATP-敏感的鉀通道開啓、adenylate cyclase 或 guanylate cyclase 活化無關。

QPME (10, 20 mM) 類似 IBMX (3, 6 mM)，能使 forskolin 的對數濃度-反應曲線向左平行移動，而於 20 mM 下亦可使 nitroprusside 的對數濃度-反應曲線向左移動，使 forskolin 及 nitroprusside 的 pD2 值增加，顯示其可能有抑制 phosphodiesterase (PDE) 的作用。由 PDE 活性的直接測定,得知 QPME (50-300 mM) 能抑制 cAMP-PDE 及 cGMP-PDE 的活性,並於 50 及 100 mM 時對 cAMP-PDE 的抑制程度有意義的大於 cGMP-PDE，因此推測 QPME 在此二種濃度下對 cAMP-PDE 的抑制能力較強。

英文摘要

The tracheal relaxant activities and action mechanisms of quercetin methyl ether derivatives, including quercetin 4'-methyl ether (tamarixetin), quercetin 3,4',7-trimethyl ether (ayanin), quercetin 3,3',4',7-tetramethyl ether (QTME) and quercetin 3,3',4',5,7-pentamethyl ether (QPME) were analyzed and compared with our previous studies of quercetin and quercetin 3-methyl ether to understand their structure-activity relationship (SAR). The above querce\9?methyl ether derivatives concentration-dependently reled the histamine (30 mM)-, carbachol (0.2 mM)- and KCl (30 mM)-induced precontractions of isolated guinea-pig trachea. Roughly, according to their IC25s, the order of their relaxant activity was QPME, quercetin 3-methyl ether > quercetin, ayanin > tamarixetin > QTME. The SAR was concluded as follows: (a) Methylation at position 3 or 5 on quercetin, for example quercetin to quercetin 3-methyl ether and QTME to QPME, largely increased their relaxant activity. (b) Methylation at position 3' or 4' on quercetin,uch as ayanin to QTME and quercetin to tamarixetin, reduced their relaxant activity; and (c) The relaxant activity does not increase with the number of methoxyl group because QTME has the lowest

relaxant effect and ayanin has lower relaxant activity than quercetin 3-methyl ether.

The preincubation of the more potent quercetin methyl ether derivative, QPME, non-competitively inhibited contraction induced by cumulatively adding histamine, carbachol or KCl in isolated guinea-pig trachea. In carbachol and KCl, the pD2' values were significantly less than their -logIC50s. Therefore, the inhibitory ability of QPME on calcium release from calcium stores may be less potent than the suppression of calcium influx from extracellular fluid in carbachol- and KCl- induced contraction. QPME also n-competitively inhibited contractions of the trachealis induced by cumulatively adding calcium into high potassium (60 mM)-Ca2+ free medium in the trachealis. After maximal relaxation on histamine (30 mM)-induced precontraction by nifedipine (10 mM), QPME caused further relaxation of the trachealis. The result suggests that QPME may have other relaxant mechanisms in addition to inhibiting voltage (VOC) and/ or receptor operated calcium channels (ROC) in the trachealis. However, its relaxant response was not fected by the removal of epithelial cells or by the presences of propranolol (1 mM), glibenclamide (10 mM), methyleneblue (25 mM) and 2',5'-dideoxyadenosine (10 mM). Therefore, its relaxing effect may not be related to epithelium derived relaxing factor(s), activation of b-adrenoreceptor, opening of ATP-sensitive potassium channels, or activation of guanylate cyclase or adenylate cyclase.

Similar to IBMX (3-6 mM), QPME (10, 20 mM) parallelly leftward shifted the log concentration-response curve of forskolin, and at 20 mM, QPME also leftward shifted the log concentration-response curve of nitroprusside, and reduced the pD2 values of forskolin or nitroprusside. It suggests that QPME may inhibit phosphodiesterase (PDE). In the assay of PDE activity, QPME (50-300 mM) inhibited both cAMP- and cGMP-PDE. In the presence of QPME 50 and 100 mM, the cAMP-PDE activity was significantly lower than cGMP-E, suggesting that QPME has stronger inhibition in cAMP-PDE than in cGMP-PDE activity at 50 and 100 mM.