• 系統編號	RC8705-0560		
• 計畫中文名稱	類黃鹼素之氣管鬆弛作用及其構造：活性的關係		
• 計畫英文名稱	Tracheal Relaxant Effects of Flavonoids and Their Structure-Activity Relationships		
• 主管機關	行政院國家科學委員會	• 計畫編號	NSC86-2314-B038-039
• 執行機構	台北醫學院藥理科		
• 本期期間	8508 ~ 8607		
• 報告頁數	0 頁	• 使用語言	中文
• 研究人員	柯文昌 Ko, Wun-Chang		
• 中文關鍵字	氣管擴張作用；類黃鹼素；磷酸雙酯；結構活性關係；黃酮；芹菜素；黃酮醇；查酮		
• 英文關鍵字	Tracheal relaxant effect；Flavonoid；Phosphodiesterase；Structure activity relationship (SAR)；Flavone；Apigenin；Flavonol；Genistein；Narigenin；Chalcone		
• 中文摘要	我們分析類黃鹼素各類,包括 Flavone 類(如 Flavone 及 Apigenin)、Flavonol 類(如 Flavonol)、Isoflavone 類(如 Genistein)、Flavanone 類(如 Naringenin)、Chalcone 類(如 Chalcone)之氣管鬆弛活性,並進一步探討它們的作用機轉,以瞭解它們的 Structure-activity relationship(SAR)。上述六種 Flavonoids 對 Histamin(30.mu.M)、Carbachol(0.2.mu.M)、KCl(30mM)及 Leukotriene D/sub 4/(10nM)預縮的離體天竺鼠氣管,產生劑量依存性的鬆弛作用,由其 IC/sub 50/得知其活性大致依序爲 Flavone、Apigenin、Genistein>Flavonol>Narigenin>Chalcone,其 SAR 如下:(a)Flavone 類上的第 3 位以-OH group 取代變成 Flavonol 類,如 Flavone 變成 Flavonol,會使活性下降;(b) Flavone 類上的第 2 位和第 3 位間的雙鍵飽和後變成 Flavanone 類,如 Apigenin 變成 Naringenin,會使活性下降;(c)Flavone 類 C-ring 上的 Ether linkage 斷裂後變成 Chalcone 類,如 Flavone 變成 Chalcone,則活性大大的降低;及(d)Flavone 類變成 Isoflavone 類,如 Apigenin 變成 Genistein,不影響其活性。 上述六種 Flavonoids 中較強的三種 Flavone,Apigenin 或 Genistein 預處理均能非競爭性地對抗累加 Histamine、Carbachol 或 KCl 引起的收縮,它們的 pD/sub 2/'值大致上均有意義地小於它們的-IogIC/sub 50/,顯示三者抑制內鈣釋放的能力小於抑制外鈣內流的能力。在高鉀(60mM)無鈣溶液中,它們也能非競爭性地抑制累加外鈣引起的收縮,也對 Histamine(30.mu.M)預縮而 Nifedipine(10.mu.M)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 calcium channels(ROC)外,尚有其他的鬆弛機轉。然而其鬆弛反應不因上皮細胞去除或 Propranolol (1.mu.M)、Glibenclamide(10.mu.M)、Methylene blue(25.mu.M)及 2',5'- dideoxyadenosine (10.mu.M)存在的影響,表示其鬆弛作用與 Epithelium- derived relaxing factor(s)、.beta.-adrenoceptor 受體活化、ATP-敏感的鉀通道開啓、Adenylate cyclase 或 Guanylate cyclase 活化無關。 類似 IBMX(3-6.mu.M),Flavone (12.5-25.mu.M)、Apigenin(15-30.mu.M)及 Genistein(17.5-35.mu.M)能劑量依存性地使 Forskolin		

或 Nitroprusside 的對數劑量-反應曲線向左平行移動,而使 Forskolin 或 Nitroprusside 的 IC/sub 50/及其劑量比(Dose ratio)減少。Flavone 或 Apigenin 但非 Genistein,對 Nitroprusside 的劑量比有意義地小於對 Forskolin 的劑量比,因此推測前二者對 cGMP-phosphodiesterase(PDE)的抑制較具選擇性。利用酵素免疫分析法測定,得知在三種 Flavonoids(150.mu.M)能使氣管平滑肌 cAMP 和 cGMP 之含量有意義的增加,其中 Flavone 或 Apigenin 但非 Genistein,使 cGMP 增加的倍數也有意義地大於 cAMP 增加的倍數。此結果支持 Flavone 類(如 Flavone 或 Apigenin),但不是 Isoflavone 類(如 Genistein),對 cGMP-PDE 的抑制較具選擇性。

- 英文摘要

The tracheal relaxant activities and action mechanisms of flavonoids, including various classes such as flavones (i.e. flavone and apigenin), flavonols (i.e. flavonol), isoflavones (i.e. genistein), flavanones (i.e. naringenin) and chalcones (i.e. chalcone) were analyzed to understand their structure-activity relationship (SAR). The above six flavonoids dose-dependently relaxed the histamine (30.mu.M)-, carbachol (0.2.mu.M)-, KCl (30mM)-, and leukotriene D/sub 4/(10nM)-induced precontractions of isolated guinea-pig trachea. Roughly, according to their IC/sub 50/s, the order of their relaxant activity was flavone, apigenin, genistein> flavonol>naringenin>chalcone. The SAR was concluded as follows: (a) The substitution of -OH group at position 3 on flavones to form flavonols, for example flavone to flavonol, reduced their relaxant activity; (b) The saturation of the double bond between position 2 and 3 on flavones to form flavanones, such as apigenin to naringenin, also reduced their relaxant activity; (c) The opening of C-ring from ether linkage on flavones to form chalcones, such as flavone to chalcone, largely reduced their relaxant activity; and (d) Change from flavones to isoflavones, such as apigenin to genistein, did not affect their relaxant activity. The preincubation of these three more potent flavonoids, flavone, genistein and apigenin among the above six, non-competitively inhibited contraction induced by cumulatively adding histamine, carbachol or KCl in isolated guinea-pig trachea. In general, their pD/sub 2/' values were significantly less than their -logIC/sub 50/s. Therefore, their inhibitory abilities on calcium release from calcium stores may be less potent than their suppression of calcium influx from extracellular fluid. They also non-competitively inhibited contractions of the trachealis induced by cumulatively adding calcium into high potassium (60mM)-Ca/sup 2+/free medium in the trachealis. After maximal relaxation on histamine (30.mu.M)-induced precontraction by nifedipine (10.mu.M), they caused further relaxation of the trachealis. The result suggests that they may have other relaxing mechanisms in addition to inhibiting voltage (VOC) and/or receptor operated calcium channels (ROC) in the trachealis. However, their relaxant responses were not affected by the removal of epithelial cells or by the presences of propranolol (1.mu.M), glibenclamide (10.mu.M), methyleneblue (25.mu.M) and 2',5'-dideoxyadenosine (10.mu.M). Therefore, their relaxing effects may not be related to epithelium derived relaxing factor(s), activation of .beta.-adrenoreceptor, opening of ATP-sensitive potassium channels, or activation of guanylate cyclase or adenylate cyclase. Similar to IBMX (3-6.mu.M), flavone (12.5-25.mu.M), genistein (17.5-35.mu.M) and apigenin (15-30.mu.M) dose-dependently and parallelly to the left shifted the log dose-response curve of forskolin or nitroprusside, and reduced the IC/sub 50/s and dose ratios of forskolin or nitroprusside. The dose ratios of nitroprusside in the presence of flavone or apigenin, but not genistein, were significantly less than those of forskolin. It suggests that the former two may selectively inhibit cGMP-phosphodiesterase (PDE). Moreover, these three flavonoids (150.mu.M) significantly enhanced cAMP and cGMP contents in the trachealis determined by using enzyme immunoassay. Flavone or apigenin, but not genistein, significantly enhanced more cGMP content than that of cAMP. The result supports the context that flavones (flavone or apigenin) but not isoflavones (genistein), may

selectively inhibit cGMP-PDE.