• 系統編號	RC9001-0163
• 計畫中文名稱	氣球擴張術引起老鼠動脈血管內膜增生的研究:比較 Triflavin 和抗 σvβ3 單源抗體的相對作用機轉及活性(I)
• 計畫英文名稱	Study of Neointimal Hyperplasia of Balloon Injured Rat Carotid Arteries: Comparison of the Mechanisms and Relative Activities of Triflavin with anti-.alpha./sub v/.beta./sub 3/ Monoclonal Antibody (I)
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC89-2320-B038-001
• 執行機構	台北醫學院藥理科
• 本期期間	8808 ~ 8907
• 報告頁數	0 頁
• 使用語言	中文
• 研究人員	許準榕 Sheu, Joen-Rong
• 中文關鍵字	氣球擴張術；血管內膜增生；龜殼花出血性蛇毒蛋白；黏合素
• 英文關鍵字	Balloon angioplasty；Intimal hyperplasia；Triflavin；Integrin
• 中文摘要	在病人施行冠狀動脈血管造形術(Percutaneous transluminal coronary angioplasty)後,根據統計約有 40-50%的病患常會發生手術血管發生再窄化(Restenosis)的現象;意即進行手術的部位其血管管腔減小,而使心肌的缺血現象產生最後導致心肌梗塞。一般而言,血管再窄化的發生約可分爲 3 個主要步驟,依序爲(1)血管內的彈性回縮作用(Elastic recoil);(2)血栓的形成(包括血小板的附著、凝集及釋放生長因子)與發炎細胞的侵入;(3)血管中層平滑肌細胞的增生和移動以及細胞外基質蛋白(Extracellular matrix)的擴張。目前有許多的動物實驗利用各種不同的藥物來試圖減少血管再窄化的發生;包括使用抗血小板凝集藥物(如 Aspirin、Ticlopidine),抗凝血藥、鈣離子通道阻斷劑,降血脂藥物等等;但大多藥物經臨床試驗後發現效果卻不理想。 Triflavin 爲一種由出血性的蛇毒(Trimeresurus flavoviridis)中所分離的強效抗血小板凝集蛋白;它本身爲單鍵含有 70 Amino acids;在靠近 C 端位置含有 Arg-Gly-Asp(RGD)這三個 Amino acid,在 Triflavin 抑制血小板凝集過程中扮演了決定性的角色。Triflavin 的作用機轉爲競爭性的抑制 Fibrinogen 和血小板.alpha./sub IIb/.beta./sub 3/ Integrin 的結合作用,爲一種專一性的.alpha./sub IIb/.beta./sub 3/ Integrin 拮抗劑;因此在活體內亦能有效的防止血栓產生。 .alpha./sub IIb/.beta./sub 3/ Integrin 本身爲.beta./sub 3/ Integrin 的一員,屬於一種附著蛋白受體;它在體內參與了發育(Development)、發炎(Inflammation)與血栓(Thrombosis)等等。.alpha./sub v/ .beta./sub 3/ Integrin 也是.beta./sub 3/ Integrin 的一員,廣泛的存在於平滑肌細胞,內皮細胞、單核球及腫瘤細胞;在血管再窄化的過程中,有關血管平滑肌的附著和移動;內皮細胞與細胞外基質蛋白的結合,此.alpha./sub IIb/ .beta./sub 3/ Integrin 都扮演了相當重要的角色。 因此本計畫的主要目的,在探討及比較 Triflavin(.alpha./sub IIb/ .beta./sub 3/ Integrin antagonist)和 anti-.alpha./sub v/ .beta./sub 3/ Integrin 單源抗體對於氣球擴張術後引起大白鼠頸動脈血管內膜增生的抑制作用以及其個別作用機轉的探討。本計畫擬以三年的時間來探討相關的作用機

轉。在今年度的計畫中(NSC-89),我們發現在大白鼠頸動脈進行氣球擴張術引起動脈血管內皮細胞受損後,其血管新內膜的增生(Neointimal hyperplasia)情形會隨著時間的增加而增加;而血小板的凝集與血栓的生成則在第一週最爲明顯,之後則逐漸被血管平滑肌細胞的增生、移動及新內膜的增生所取代。在施行氣球擴張術後,同時利用內置式滲透壓幫浦分別開始連續給與 Triflavin 一週及二週。由實驗結果顯示,給與 Triflavin 於手術一週及二週後可明顯抑制血栓的生成及血管內膜增生;同時,Triflavin 亦可抑制因氣球擴張術所引起的 Thromboxane B/sub 2/的增加。另外,Triflavin 對氣球擴張術所引起的 Nitric oxide 及 Cyclic GMP 的增加並無明顯的影響。

- 英文摘要

Recent large-scale trials of percutaneous transluminal coronary angioplasty (PTCA) have emphasized the frequency of stenosis recurrence about 40-50% of patients with percutaneous treatment. Restenosis is the decrease of the vessel lumen at the site of the procedure, thereby leading to induce ischemia. The major steps in the development of restenosis are: (1) elastic recoil; (2) subclinical development of thrombosis (platelet adhesion, aggregation, and release of growth factors) with inflammatory cell infiltration, and (3) medial smooth muscle cell proliferation and migration, followed by extracellular matrix expansion. There are numerous agents have been tested in animal models, such as antiplatelet drugs (aspirin, ticlopidine); antithrombotic drugs (hirudin, heparin); calcium-channel blockers; immunosuppressive agents, hypolipidemic agents; until recently none has translated into benefit in large-scale clinical trials. Triflavin, a potent platelet aggregation inhibitor, was purified from the venom of Trimeresurus flavoviridis. Its sequence contains the Arg-Gly-Asp (RGD) in the carboxyl terminal domain. The RGD sequence of triflavin plays an important role in mediating the binding of triflavin towards glycoprotein IIb/IIIa complex (.alpha./sub IIb/.beta./sub 3/ integrin). Triflavin inhibits platelet aggregation by interfering with the interaction of fibrinogen with the .alpha./sub IIb/.beta./sub 3/ integrin. It is an effective agent in the prevention of thromboembolism. .alpha./sub IIb/.beta./sub 3/ belongs a .beta./sub 3/integrin family, involves in cell development, inflammation and thrombosis. .alpha./sub v/.beta./sub 3/ integrin also belongs a .beta./sub 3/ integrin family, it is heavily expressed by numerous cells, including endothelial cells, monocytes, smooth muscle cells and melanoma cells. The .alpha./sub v/.beta./sub 3/ integrin is thought to play a major role in the adhesion and migration of smooth muscle cells and endothelial cells on extracellular matrices. The present project was designed to determine the effect of triflavin (.alpha./sub IIb/.beta./sub 3/ integrin antagonist) in neointimal hyperplasia of balloon injured rat carotid arteries, and to compare the relative activities and mechanisms of anti-.alpha./sub v/.beta./sub 3/ integrin monoclonal antibody. In the first year of study, we found that the formation of neointimal hyperplasia was increased (time-dependently) after angioplasty. Platelet aggregation and thrombus formation were found in the first week, which may be followed by vascular smooth muscle cell proliferation, migration and neointimal formation. Triflavin was administered by a continuous intravenous infusion for 1-2 weeks through an implanted osmotic pump after angioplasty. Our result shows that triflavin treatment inhibited effectively the thrombus and neointimal formation within 1-2 weeks after angioplasty, indicating that triflavin was effectively at prevention of neointimal hyperplasia in rats. In addition, triflavin also significantly inhibits TxB/sub 2/ formation induced by angioplasty. Whereas, triflavin did not inhibit both the nitric oxide and cyclic GMP formation induced by angioplasty.