行政院國家科學委員會專題研究計畫成果報告

計畫編號：NSC 88-2314-B-002-224

執行期限：87 年 8 月 01 日至 88 年 07 月 31 日

題目：Pentoxifylline 對實驗性慢性腎小球腎炎的影響

主持人：蔡敦仁 執行機構及單位名稱：國立台灣大學醫學院內科

一、 中文摘要

本研究室曾發現pentoxifylline (以下簡稱PTX) 可以在老鼠實驗性膈細胞增生性腎炎降低蛋白尿，抑制膈細胞增生及間質蛋白累積。因此，此藥對於腎臟病可能具有療效。我們進一步擴大觀察，對另外的實驗性腎炎是否具有效果。首先在急性腎炎，我們同樣在膈細胞增生型腎炎的模式，併用 PTX 與血管張力素轉換酶抑制劑(ACEI)lisinopril (簡稱 LSP)，探討是否比單獨使用 PTX 更有療效，其次在慢性的實驗模式，取掉一邊腎臟後，注射單株抗體引發慢性腎炎，再探討 PTX 是否具有療效。

結果發現，合用 PTX 與 lisinopril 比單獨使用 PTX，其腎臟組織切片有較明顯的改善，利用分離之腎小球作測量，發現第 I 型膠原蛋白與第 III 型膠原蛋白的基因表現，在使用 PTX 與 LSP 合併組顯然比單獨使用 PTX 或單獨使用 LSP 之抑制更加明顯。表示合併使用兩種比單獨使用一種更為有效。其次，在單側腎切除後引發之慢性腎炎模式，使用 PTX 之後，腎小球內膈細胞的增生，以及細胞外間質的增加都有明顯減少。結論：PTX 如果與 ACEI 併用效果可能更佳。另 PTX 對於慢性腎炎也可能具有療效。

二、 英文摘要

We previously found that pentoxifylline (PTX) decreased proteinuria, inhibit mesangial cell (MC) proliferation and extracellular matrix (ECM) accumulation in a thy-1.1 antibody induced mesangial proliferative glomerulonephritis (MsPGN). We further extended our investigation by doing 2 experiments. First, we combine PTX and an angiotensin converting enzyme inhibitor (ACEI)-lisinopril (LSP) in MsPGN model and compare the effect with single drug use (either PTX or LSP alone). Second, we remove one kidney and injected anti-thy1.1 antibody to produce a chronic GN model. PTX was given for 3 months. We found that combined PTX and LSP had better effect than single drug use in respects of MC proliferation and ECM accumulation. The type I and type III collagen gene expression was inhibited best in combined group than either group using single drug. In uninephrectomized and thy-1.1 antibody induced CGN model, PTX treatment group showed less MC proliferation and ECM accumulation.

We conclude that combined PTX and LSP have better effect than single drug use. PTX may also have beneficial effect in retarding progression of CGN.

三、 緣由與目的

Accumulation of glomerular macrophages, proliferation of mesangial cells (MCs), and deposition of extracellular matrix proteins are pathological hallmarks of glomerulonephritis. We previously reported that a clinically available nonselective inhibitor of cyclic 3', 5'-nucleotide phosphodiesterase, pentoxifylline (PTX), inhibits proliferation of cultured rat MCs, as well as collagen production by these cells. We also proved that PTX can attenuate experimental mesangial proliferative glomerulonephritis in respects of urinary protein excretion, glomerular cellularity, and glomerulosclerosis. We further investigate the effect of PTX on other models of renal disease, we performed 2 sets of experiments. First, we performed an acute experiment. Because angiotensin II converting enzyme inhibitor(ACEI) was reported able to reduce renal TGF-β1 in experimental mesangial proliferative glomerulonephritis, we combined PTX and lisinopril to treat the experimental mesangial proliferative glomerulonephritis and compare with either PTX or LSP alone. Second, we also studied the effect of PTX in a chronic glomerulonephritis model by injecting thy-1.1 antibody to uninephrectomized rats.

四、 結果與討論

In the 1st experiment; we compared thy-1.1 antibody induced glomerulonephritic rats treated with PTX alone (iv infusion), LSP alone (oral) or PTX+LSP for 1 week. Glomerular mRNA levels of type I (α1) collagen and type III (α1) collagen was inhibited mostly in PTX + LSP group, compared with either PTX or LSP group (Fig1). Pathology showed less mesangial proliferation and matrix accumulation in PTX+LSP group, compared with other 2 groups (Fig.2-5). In the second experiment, rats were uninephrectomized and then injected with 250 μg mouse anti-rat thy1-1 monoclonal antibody. PTX was given thru oral route. Rats were sacrified after 3 months. We observed less glomerular mesangial cell proliferation and extracellular matrix accumulation in the pentoxifylline treated group.(Fig. 6, 7)

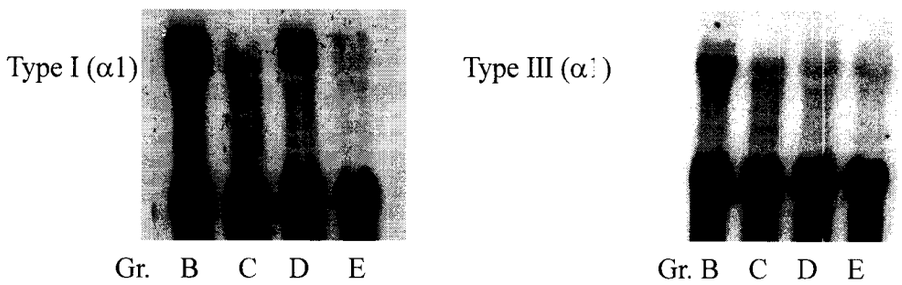

Fig. 1 Collagen gene expression was mostly inhibited in combined group (E) than PTX alone (C) or LSP alone (D)

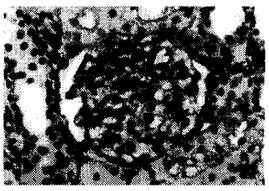

Fig 2
Anti-Thy 1-1 megangial proliferative GN (MsPGN)：
marked mesangial cell proliferation and expanded extracelluar matrix

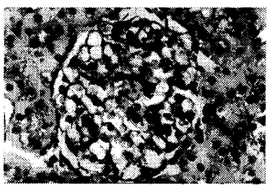

Fig 3
PTX treatment alone (in MsPGN)
Decreased cell proliferation and extracellular matrix accumulation

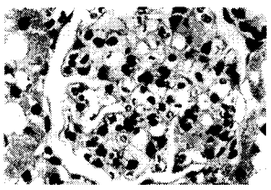

Fig 4
Lisinopril treatment alone in MsPGN：
Decreased cell proliferation and extracellular matrix accumulation

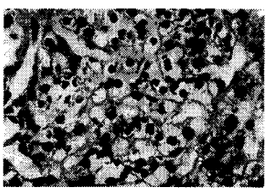

Fig 5
Pentoxifylline+Lioinopril treatment in MsPGN：
Decreased cell proliferation and extracellular matrix accumulation

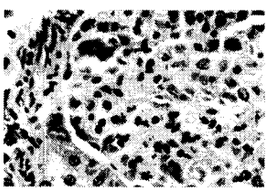

Fig 6
Chronic glomerulonephritis model (CGN)：
Increased mesangial cell proliferation and expaned extracellular matrix, periglomerular fibroblast-like cell proliferation

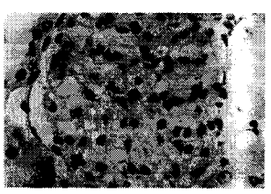

Fig 7
Pentoxifylline treatment in CGN：
Less increased cell proliferation.
Less increased extracellular matrix

These results suggested that PTX, if combined with ACEI, may have better effect than single drug use. Besides, PTX also have beneficial effect in a chronic GN process.

五、計畫成果自評

These study results reinforce the clinical potential of PTX in treating renal disease. Our results accomplished major part of the original goal. Besides, we further found that combined therapy with ACEI may have better effect. This has never been reported before. Such findings disclosed a possibility that, in the future, cocktail therapy may provide a good way to achieve remission of chronic progressive renal disease.

六、 參考文獻

1. Chen YM, Chien CT, Tsai-Hui MI, et al. Pentoxifylline attenuates experimental mesangial proliferative glomerulonephritis. Kidney Int 1999;56:932-943
2. Nakamura T, Obata JE, Kimura H, et al. Blocking angiotensin II ameliorates proteinuria and glomerular lesions in progressive mesangioproliferative glomerulonephritis. Kidney Int 1999;55:877-889
3. Tsuboi Y, Shankland SJ, Grande JP, Walker HJ, Johnson RJ, Dousa TP. Suppression of mesangial proliferative glomerulonephritis development in rats by inhibitors of cAMP phosphodiesterase isozymes type III and IV. J Clin Invest 1996;98:262-270.
4. Steinmann-Niggli K, Ziswiler R, Kung M, Marti H-P. Inhibition of matrix metalloproteinases attenuates anti-Thy 1.1 nephritis. J Am Soc Nephrol 1998;9:397-407.
5. Zoja C, Abbate M, Corna D, et al. Pharmacologic control of angiotensin II ameliorates renal disease while reducing renal TGF-β1 in experimental mesangioproliferative glomerulonephritis. Am J Kidney Dis 1998;31:453-463.
6. Peterson TC: Pentoxifylline prevents fibrosis in an animal model and inhibits platelet-derived growth factor driven proliferation of fibroblasts. Hepatology 1993;17:486-493.
7. Bennett W, Elziwga LW et al: The effects of pentoxifylline on experimental chronic cyclosporine nephrotoxicity. Transplantation 1992;54:1118-1120.
8. Guerrero-Romero F, Rodriguez-Moran M, Paniagua-Sierra JR, Garcia-Bulnes G, Ramirez M, Amato D: Pentoxifylline reduces proteinuria in insulin-dependent and non insulin-dependent diabetic patients. Clin Nephrol 1995;43:16-21.
9. Tsai TJ, Lin RH, Chang CC, Chen YM, Chen CF, Ko FN, Teng CM: Vasodilator agents modulate rat glomerular mesangial cell growth and collagen synthesis. Nephron 1995;70:91-99.
10. Remuzzi G, Zoja C, Gagliardini E, et al. Combining an antiproteinuric approach with mycophenolate mofeltil fully suppresses progressive nephropathy of experimental animals. J Am Soc Nephrol 1999;10:1542-1549.