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• 計畫中文名稱	第二型環氧化脢抑制劑防止單側輸尿管阻塞引起之腎纖維化 是經由誘發鐵血紅素氧脢
• 計畫英文名稱	Prevention of Renal Fibrosis in Unilateral Ureteral Obstruction by Cyclooxygenase-2 Inhibitor Is Mediated through Heme Oxygenase-1 Induction
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• 中文關鍵字	第二型環氧化脢抑制劑; 轉型生長因子-beta; 鐵血紅素氧脢; 腎臟纖維化症
• 英文關鍵字	COX-2 inhibitor; TGF-beta; HO-1; Renal fibrosis

• 中文摘要

腎小管及間質纖維化(tubulointerstitial fibrosis)是末期腎臟病主要病理特徵，也是造成腎功能惡化的重要因素，但是至目前仍無適當的治療方法來減緩腎纖維化的進行。在 5／6 腎臟切除之大白鼠模型，以第二型環氧化脢抑制劑治療顯著減少尿蛋白及腎纖維化。本研究旨在探討第二型環氧化脢抑制劑 celecoxib 是否可減緩大白鼠單側輸尿管結紮導致的腎纖維化及其機轉是否經由誘發鐵血紅素氧脢(hemeoxygenase-1)。成年 Sprague-Dawley 大鼠於單側輸尿管結紮後分爲四組:(1)每日灌食第二型環氧化脢抑制劑 celecoxib(10 毫克／公斤)，(2)每日灌食等體積安慰劑，(3)手術前一天及術後第四天於腹腔注射錫前脢喀紫質(SnPP,10μmol／kg)且每日灌食 celecoxib(10 毫克／公斤)，(4)手術前一天及術後第四天於腹腔注射生理食鹽水且每日灌食 celecoxib(10 毫克／公斤)。同時有二組大鼠接受假手術，一組給予 celecoxib、另一組給安慰劑。所有大鼠在術後第七天安樂死取出腎臟。利用 periodicacid-Schiff 染色及第一型膠原蛋白(collagentypeI)、α-平滑肌動蛋白(α-SMA)及轉型生長因子-β(TGF-β)免疫染色來分析腎纖維化病變。研究結果顯示，與假手術大鼠比較，單側輸尿管結紮導致腎小管萎縮、腎間質單核球細胞浸潤及纖維化病變，而 celecoxib 治療可顯著減緩這些病變。celecoxib 也顯著減少第一型膠原蛋白、α-SMA 及 TGF-β 蛋白在輸尿管阻塞腎臟的表現。但是以錫前脢喀紫質前處理抑制鐵血紅素氧脢性，則發現 celecoxib 對輸尿管阻塞腎臟纖維化的保護作用消失。本研究顯示了第二型環氧化脢抑制劑 celecoxib 在避免腎纖維化上具有治療的潛力，而其機轉可能與鐵血紅素氧脢誘發有關。

- 英文摘要

Tubulointerstitial fibrosis is a common feature of end-stage renal disease of various etiologies. Progression of tubulointerstitial fibrosis strongly correlated with deterioration of renal function. Transforming growth factor-beta(TGF-beta) is the putative key mediator of fibrosis in both experimental and human chronic kidney diseases. Emerging evidences suggested selective inhibition of cyclooxygenase-2 (COX-2), by counteracting the effects of TGF-beta, is renoprotective in progressive nephropathies. The purpose of this study was to determine whether celecoxib, a selective COX-2 inhibitor, reduces renal fibrosis induced by unilateral ureteral obstruction (UUO) and if this effect is mediated through heme oxygenase 1(HO-1) induction. Male Sprague-Dawley rats were subjected to UUO surgery and divided into four groups: (1) treatment with celecoxib (10mg／kg body weight) by daily oral gavage immediately after surgery (n=6), (2) treatment with vehicle (n=6), (3) inhibition of HO-1 activity by intraperitoneal (IP) injection of tin protorporphyrin (SnPP) 10.mu.mol／kg, and celecoxib treatment (n=6), (4) 0.9% saline IP injection and celecoxib treatment (n=6). Untreated and celecoxib treated sham-operated rats were also studied. All animals were euthanized at day 7 and therapeutic effects of celecoxib, with or without SnPP, on renal fibrosis were assessed by immunohistocytochemistry. Periodic acid-Schiff (PAS) staining and collagen I, alpha-smooth muscle actin(alpha-SMA), and TGF-beta immunostaining were analyzed. Compared with sham-operated rats, control UUO rats exhibited severe tubular atrophy, mononuclear cell accumulation and interstitial fibrosis, which were significantly attenuated in celecoxib-treated rats. Celecoxib treatment led to significant attenuation of renal collagen I and TGF-betaexpression and myofibroblast accumulation. However, UUO rats with SnPP administration, by inhibition of HO-1 activity, abolished the beneficial effect of celecoxib on interstitial fibrosis and tubular atrophy. In conclusion, these data indicate that, by mechanism involving HO-1 induction, the selective COX-2 inhibitor celecoxib might have therapeutic potential for prevention of renal fibrosis.