# 제 2형 당뇨모델인 db/db mice에서 CCR2 차단제 치료가 인슐린 저항성 및 당뇨병성 신증에 미치는 효과

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# CCR2 Antagonist Improves Insulin Resistance and Ameliorates Diabetic Nephropathy in Type 2 Diabetic Mice

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Monocyte chemoattractant protein-1 is a member of the CC family of chemokines, and has been reported that it has an important role in the pathogenesis of diabetic nephropathy. Recent studies suggest that blockade of CCR2 prevent the occurrence of diabetic nephropathy, which provide the crucial effect of CCR2 in development of diabetic nephropathy. However, the exact mechanism of CCR2 inhibition has not been known yet. In this study, we investigated the effect of CCR2 antagonist (RS504393: 2 mg/kg/day in mixed chaw) on insulin resistance and diabetic nephropathy in type 2 diabetic db/db mice. Interestingly, CCR2 antagonist treatment significantly decreased SBP, but there was no improvement in cardiac function assessed by echocardiogram. Although FPG did not show significant difference, insulin sensitivity assessed by intraperitoneal insulin tolerance test (IP-ITT) was significantly improved. Furthermore, plasma insulin levels and HOMA-IR showed significantly improved by CCR2 inhibition. In accordance with this metabolic improvement, plasma cholesterol and triglyceride levels were markedly decreased in CCR2 antagonist treatment. In addition, CCR2 inhibition decreased epididymal fat mass and induced the phenotypic change of adipocyte, which showed differentiated form of adipocytes. In line with the improvement of phenotypic change in adipocytes, MCP-1 expression and LPO levels in adipose tissue showed significantly lower levels in CCR2 antagonist treated mice. Associated with improvement in metabolic parameters, CCR2 inhibition significantly decreased urinary albumin excretion after 1month of treatment, and showed significantly decreased serum Cr and improvement in creatinine clearance. Furthermore, CCR2 antagonist treatment markedly suppressed glomerulosclerosis and pro-fibrotic cytokine expression and protein synthesis in diabetic kidney including TGF$\beta$1, PAI-1, MCP-1 and type IV collagen. Interestingly, urinary isoprostane and LPO levels in kidney showed significantly lower levels after CCR2 inhibition. In addition, CCR2 inhibition improved the gene expression profile involved in lipid metabolism in the diabetic kidney, and improved cholesterol and triglyceride content in the kidney. From these results, we suggest that CCR2 antagonist treatment improves insulin resistance through modulation of adipocytokine synthesis from adipose tissues, and improves renal function through both metabolic and direct effect in the kidney, finally leading to the protective effect for the progression of diabetic nephropathy in type 2 diabetic mice.

**Key Words :** 당뇨병성 신증, CCR2 차단제 Diabetic nephropathy, CCR2 antagonist