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제2형 당뇨모델인 db/db mice에서 Cannabinoid receptor 1(CB-1) antagonist가 인슐린 저항성 및 당뇨병성 신증에 미치는 영향

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Cannabinoid Receptor 1 Antagonist Improves Insulin Resistance and Ameliorates Diabetic Nephropathy in db/db Mice

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Objectives: The CB1 receptor has an important role in the pathogenesis of obesity and insulin resistance. Recent studies suggest that the glomerular expression of CB1 receptor is increased in obese zucker rats, and associated with abnormal renal lipid metabolism. However, the exact mechanism and role of CB1 receptor inhibition in diabetic nephropathy has not been known yet.

Methods: In this study, we investigated the effect of CB1 receptor antagonist (CB1RA, SR141716: 10 mg/kg/day in drinking water) on insulin resistance and diabetic nephropathy in type 2 diabetic db/db mice.

Results: Interestingly, CB1RA treatment significantly decreased food intake. Although fasting plasma glucose (FPG) did not show significant difference, insulin sensitivity and glucose intolerance assessed by intraperitoneal insulin tolerance test (IP-ITT) and oral glucose tolerance test (OGTT) was significantly improved. Plasma insulin levels and HOMA-IR were also improved by CB1AR treatment. In accordance with these metabolic improvements, plasma cholesterol, triglyceride and isoprostane levels were markedly decreased by CB1AR treatment. In addition, its treatment decreased epididymal fat mass and induced the phenotypic change of adipocyte, and decreased hepatic steatosis. Simultaneously, LPO levels in adipose tissue and liver also showed significantly lower values in treated mice than that in control mice. Furthermore, CB1AR improved renal hypertrophy and decreased urinary albumin excretion only by 1 month of treatment, and showed significantly decreased serum creatinine level. Interestingly, CB1RA markedly suppressed urinary isoprostane, LPO levels of kidney, lipids contents of cholesterol and triglyceride of kidney, with an improvement of renal glomerulosclerosis in diabetic mice.

Conclusions: From these results, we suggest that CB1RA improves insulin resistance and oxidative stress in adipose tissue and hepatic 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 신질환, 카나비노이드수용체 길항체
Cannabinoid receptor 1(CB-1) antagonist, Diabetic nephropathy