# Diabetic Nephropathy: Do Cannabinoids Contribute?

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The current standard of care for diabetic nephropathy is optimization of glycemic control and blood pressure together with the use of renin-angiotensin system inhibitors, which confer benefit over and above their antihypertensive actions. The effectiveness of these treatments has contributed to the lower age-adjusted diabetes-related incidence of end-stage renal disease in the last 10–15 yr (1). However, diabetic nephropathy remains the commonest cause of end-stage renal disease in many Western countries including the United States, and its incidence is also increasing in the developing world. This is due to a combination of the dramatically increasing worldwide prevalence of diabetes and the fact that the above treatments often delay rather than prevent progression of nephropathy. In 2009, 44% of new cases of end-stage kidney disease in the United States were attributable to diabetes (2), whereas the number of new cases of diabetes-related end-stage kidney disease in Australia increased by two thirds in those aged over 55 yr from 2000–2007 (3), which is largely attributable to patients with type 2 diabetes. These observations underlie the need for new treatment modalities, and indeed, many diverse options are being pursued (4). In this context, the study by Nam *et al.* (5) in this issue explores the potential role of cannabinoid receptor 1 blockade in ameliorating nephropathy in a mouse model of type 2 diabetes.

Endocannabinoids are arachidonic acid derivatives that regulate energy metabolism (6). They are endogenous ligands for two main receptors, the cannabinoid receptor 1 (CB1) and CB2. The highest concentrations of CB1 receptor are found in the central nervous system where they control feeding behavior and energy expenditure (6, 7). However, CB1 receptors are also expressed in peripheral tissues, including adipose tissue, skeletal muscle, liver, and pancreas, and some of their effects on glucose and lipid metabolism are mediated peripherally (6, 7). Increased activation of the CB1 system is associated with obesity, and there has been intense interest in using CB1 blockade to treat this condition (8). Concomitantly, there is evidence that these agents improve metabolic outcomes such as insulin resistance, glucose intolerance, and dyslipidemia, although the exact mechanisms remain controversial (9). After a series of successful clinical trials, the CB1 antagonist rimonabant (also known as SR141716) was marketed in Europe as an antiobesity agent; however, it was withdrawn shortly thereafter because of psychiatric side effects including anxiety, depression, and suicidal ideation, and it was never approved by the U.S. Food and Drug Administration. This agent acts centrally as well as peripherally, and there is renewed interest in the potential efficacy of CB1 blockers that do not enter the central nervous system and are therefore less likely to have these side effects (8).

CB1 receptors have also been identified in kidney cells including podocytes and proximal tubule cells. CB1 receptor blockade ameliorated the development of renal disease in obese Zucker rats and after cisplatin treatment in mice (10). Of particular relevance to the current paper (5), CB1 receptor expression was increased in podocytes of streptozotocin-treated mice, a model of type 1 diabetes (11). Blockade of CB1 using AM251, an inhibitor structurally similar to SR141716, had no effect on glycemia or blood pressure but reduced albuminuria and preserved levels of slit diaphragm proteins in podocytes. In contrast, fibrogenesis and glomerular hypertrophy were not affected by this inhibitor.

The current paper (5) studied the effects of SR141716 in db/db mice, a model of type 2 diabetes. SR141716 im-

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Abbreviation: CB1, Cannabinoid receptor 1.

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proved the plasma lipid profile, reduced glucose intolerance and insulin resistance, and transiently decreased glycated hemoglobin in the diabetic mice. Similarly to the study in type 1 diabetes (11), podocyte CB1 receptor expression was increased in this diabetic model, and the inhibitor decreased albuminuria. However, in contrast to that study, SR141716 reduced diabetes-induced up-regulation of type IV collagen and the profibrotic TGF-$\beta$. SR141716 decreased renal lipid accumulation and peroxidation as well as proinflammatory cytokine expression. SR141716 may therefore decrease kidney damage by improving the systemic metabolic derangement as well as decreasing renal lipotoxicity, oxidative stress, and inflammation.

In addition to its renal effects, the present study showed that CB1 receptor blockade decreased hepatic steatosis, aortic medial hyperplasia, and cardiac fibrosis. Another study showed that genetic or chemical CB1 receptor blockade also ameliorates retinal damage in streptozotocin-induced diabetes (12). On the face of it, a drug that ameliorates both insulin resistance and pathological pathways leading to diabetic complications sounds like a panacea. However, answers to a number of pertinent questions will enhance our understanding of the effects of CB1 receptor blockade and its therapeutic potential. Does the differential effect on renal fibrosis in models of type 1 and type 2 diabetes reflect true differences in the pathophysiology of nephropathy in these diseases, or is it a reflection of the specific animal models used in these studies? To what extent are the observed improvements in renal damage due to metabolic effects compared with direct effects on cells within the kidney? To what extent are the metabolic effects mediated centrally *vs.* peripherally? This is a critical question with respect to developing a therapeutic because SR141716 or rimonabant, the agent used in this study, acts at both sites and has already been withdrawn from human use because of psychiatric side effects. As mentioned above, peripherally restricted agents are in development (8), and their efficacy in diabetes will need to be studied. Specificity of an inhibitor for CB1 over CB2 receptors is also important, because activation of the latter may be protective against diabetic nephropathy (13). Finally, findings in animal models of diabetic nephropathy have not always translated to the clinical setting, further reinforcing the requirement for the development of an appropriate CB1 receptor inhibitor that will need to be tested extensively in humans.

Notwithstanding these challenges, studies such as this one provide hope that more effective treatments are on the horizon for diabetic nephropathy, which remains a major cause of morbidity and mortality in patients with diabetes.

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