**Review**

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The emerging role of the endocannabinoid system in the pathogenesis and treatment of kidney diseases

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**Abstract:** Endocannabinoids (eCBs) are endogenous lipid ligands that bind to cannabinoid receptors that also mediate the effects of marijuana. The eCB system is comprised of eCBs, anandamide, and 2-arachidonoyl glycerol, their cannabinoid-1 and cannabinoid-2 receptors (CB1 and CB2, respectively), and the enzymes involved in their biosynthesis and degradation. It is present in both the central nervous system and peripheral organs including the kidney. The current review focuses on the role of the eCB system in normal kidney function and various diseases, such as diabetes and obesity, that directly contributes to the development of renal pathologies. Normally, activation of the CB1 receptor regulates renal vascular hemodynamics and stimulates the transport of ions and proteins in different nephron compartments. In various mouse and rat models of obesity and type 1 and 2 diabetes mellitus, eCBs generated in various renal cells activate CB1 receptors and contribute to the development of oxidative stress, inflammation, and renal fibrosis. These effects can be chronically ameliorated by CB1 receptor blockers. In contrast, activation of the renal CB2 receptors reduces the deleterious effects of these chronic diseases. Because the therapeutic potential of globally acting CB1 receptor antagonists in these conditions is limited due to their neuropsychiatric adverse effects, the recent development of peripherally restricted CB1 receptor antagonists may represent a novel pharmacological approach in treating renal diseases.

**Keywords:** CB1 receptor; CB2 receptor; diabetic nephropathy; endocannabinoids; obesity; renal function.

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The endocannabinoid system

The recreational, psychoactive, and medicinal effects of marijuana, many of which have important therapeutic potentials, have been recognized for thousands of years [1]. Yet, it is only in the last several decades that our understanding of these effects had grown following some landmark discoveries in the field of cannabinoid research. To date, more than 60 plant-derived cannabinoid molecules have been identified in marijuana [2], among which only Δ⁹-tetrahydrocannabinol (THC) is responsible for its psychoactive properties [3]. This initial discovery has allowed the synthesis of structurally modified molecules that have been used to study structure-activity relationships and reveal tight structural and steric selectivity in the biological actions of cannabinoids. Indeed, it took more than two decades to identify the THC binding site in the brain [4], which was later cloned and named cannabinoid-1 (CB1) receptor [5]. In addition to the brain-type CB1 receptor, a second cannabinoid receptor was identified in lymphoid tissue and was named CB2 [6]. Both CB1 and CB2 receptors, which share a low level (44%) of sequence homology [6], are G protein-coupled receptors that mainly signal via G\(_i/o\) proteins, even though they may also activate G\(_s\), G\(_{q/11}\), and G protein-independent signaling pathways [7]. These receptors are expressed in the brain [8–10], liver [11, 12], skeleton [13, 14], kidney [15], and many other tissues (reviewed in [16]).

The existence of specific receptors for plant-derived molecules in mammalian cells initiated a search for specific endogenous ligands. Thus far, two extensively characterized endocannabinoids (eCBs) have been identified. The first was arachidonoyl ethanolamide (AEA, anandamide) [17], and 2-arachidonoyl glycerol (2-AG) was identified 3 years later [18, 19]. Both AEA and 2-AG are generated “on demand” from membrane phospholipid precursors in response to elevated intracellular calcium or metabotropic receptor activation [20]. Their biosynthesis may proceed along multiple parallel pathways [21, 22], which...
would make blocking their endogenous generation difficult. Unlike classical neurotransmitters, eCBs are not stored in vesicles, and the mechanism of their release from cells is not yet clear. Even when released, they remain largely membrane associated due to their hydrophobic nature and can be taken up by cells via a high-affinity uptake mechanism [23], which is followed by their enzymatic degradation. AEA is primarily catabolized by the membrane-associated fatty-acid amide hydrolase (FAAH) [24], whereas 2-AG is favorably degraded by monoglyceride lipase [25]. The CB1 and CB2 receptors, the eCBs, and enzymes/proteins involved in their biosynthesis, transport, and degradation jointly make up the “eCB system”.

The renal eCB system

The introduction of potent and selective activators and inhibitors of CB1 [26] and CB2 receptors [27] and the generation of mouse strains deficient in these receptors [28–30] have been key tools for uncovering the biological functions of the eCB system. The presence and functional importance of the renal eCB system was initially reported by Deutsch and Chin [31], who documented enzymatic activity that catalyzes AEA formation in crude rat kidney homogenates. Two years later, transcripts for the CB1 receptor were identified in human kidney [32]. Several recent reports (Table 1) have documented the presence of functional CB1 receptor in the entire kidney [15, 33–38, 40–42], including different parts of the nephron such as afferent and efferent arterioles [39], glomeruli [33, 38, 40, 42, 43], tubules [15], the loop of Henle [44], and collecting ducts [15]. It is also expressed in various subtypes of kidney cells such as podocytes [33, 41, 43, 45, 46], proximal and distal tubular epithelial cells [15, 34, 37, 38, 40, 41, 47–49], and mesangial cells [50, 54]. Moreover, CB1 receptors are expressed in human clear- and chromophobe-renal cell carcinomas, as well as in renal oncocytoma [55, 56].

Unlike CB1 receptors, there is still controversy regarding the expression of CB2 receptors in the kidney (Table 1). While several groups were unable to detect its gene and protein expression in human and rat renal tissues [15, 44], others reported that CB2 receptors are expressed in human and rat renal cortex samples, with abundant expression in podocytes [51], proximal tubule cells [34, 52, 53], and rat mesangial cells [54].

The kidney is also unique in its high basal levels of eCBs and activities of their biosynthesis and degrading enzymes [35, 38, 54, 57–60]. While the kidney cortex has similar levels of AEA and 2-AG, its medulla has more than twofold higher levels of AEA than 2-AG [60]. In agreement with these findings, the low expression levels of FAAH in the medullary cells, which is also expressed at normal levels in the glomerulus, proximal and distal tubule cells, and collecting ducts, could explain its enrichment in this renal compartment [60]. In fact, cultured renal mesangial and endothelial cells contain low levels of FAAH and are able to synthesize AEA from arachidonic acid and ethanolamine and to catabolize it by amidase activity [54]. Sampaio et al. [49] documented expression of the main enzymes responsible for eCB synthesis and degradation in immortalized epithelial cells derived from pig kidney

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proximal tubule, the LLC-PK1 cell line. The functional relevance of the renal eCB system is illustrated by recent findings that implicate it in the regulation of renal hemodynamics, inflammation, and fibrogenesis, as well as in the dysregulation of these functions in pathologic states such as diabetic nephropathy (DN) and obesity-induced renal dysfunction. This will be discussed in more detail in subsequent sections.

**eCBs and renal hemodynamics and function**

A well-known feature of AEA is that it vasodilates arteries and arterioles via the CB1 receptor (review in [61]). In view of the presence of AEA, its degrading enzyme FAAH, and the CB1 receptor in the kidney [31], Deutsch et al. [54] demonstrated the existence of these three elements in cultured renal endothelial and mesangial cells in kidney homogenates. Moreover, exogenously administered AEA has the ability to (i) vasodilate juxtamedullary afferent arterioles and (ii) stimulate the release of nitric oxide by renal endothelial cells, suggesting a key role for the eCB system in regulating renal hemodynamics. More specifically, AEA, via activation of CB1 receptors present in both afferent and efferent arterioles, increases renal blood flow and decreases the glomerular filtration rate (GFR), effects that are completely blocked by the CB1 receptor antagonists AM281 and AM251. These findings are independent of its effects on blood pressure and the sodium excretion rate [39]. Using a methylated analog of AEA, methanandamide, Li and Wang [62] showed that its intrarenal medullary infusion to anesthetized rats increases urine flow rate without changing sodium excretion and decreases mean arterial blood pressure, suggesting a regulation of body volume homeostasis and blood pressure by the renal eCB system. In a follow-up study in which the renal excitatory effect of AEA was tested following its infusion into the renal medulla, it was found that this effect is probably mediated via cyclooxygenase-2 (COX-2). Briefly, AEA or one of its COX2 metabolites, prostamide E2, shares similar properties with the vasodepressor lipid ligand medullipin, leading to increased renal blood flow, vasorelaxation, and urinary sodium excretion [60]. In regard to the specific effect of AEA on tubular sodium transport, a recent study demonstrated that AEA regulates sodium transport at the level of the medullary thick ascending limb in the kidney. In this segment, AEA (via the CB1 receptor) stimulates the production of nitric oxide, which blocks the apical Na+/H+ transporter and Na+/K+2Cl− cotransporter activity [44], thus stimulating the Na+/K+-ATPase pump located in proximal tubule cells. Recently, its activity was shown to be modulated by the CB2 agonist WIN55,212-2 and the CB1 receptor peptide agonist hemopressin. While the WIN55,212-2 stimulatory effect is mediated by protein kinase C, hemopressin increases cyclic adenosine monophosphate and stimulates protein kinase A activity [49]. Collectively, these findings highlight the importance of the eCB system in mediating renal hemodynamics and function.

**eCBs and DN**

Diabetes mellitus (DM), a chronic disease that is now reaching epidemic proportions, has been described as a catalyst for a number of conditions, most notably cardiovascular disease, retinal disease, and chronic kidney disease (CKD). Also termed DN, CKD is manifested by glomerular hypertrophy and transient hyperfiltration that lead to albuminuria, renal fibrosis, and ultimately a progressive decline in GFR [63]. In agreement with the observation that the CB1 and CB2 receptors are expressed in the kidney, several groups have tested the hypothesis of a direct signaling effect via these receptors on podocytes and mesangial and tubular cells, as well as their ability to mediate the deleterious consequences of DN.

**Role of CB1 receptors in DN**

The first direct indication for CB1 receptor involvement in DN came from a clinically relevant model of DN induced by the chemotherapeutic drug cisplatin [35]. While cisplatin-induced DN does not alter CB1 receptor gene or protein expression, it increases renal levels of AEA but not 2-AG. Either genetic deletion or pharmacological blockade of the CB1 receptor attenuates cisplatin-induced renal dysfunction. The reductions in oxidative/nitrosative stress, cell death, and infiltration of inflammatory cells within the kidney in cisplatin-treated CB1−/− mice and wild-type animals treated with the selective CB1 receptor antagonists AM281 or SR141716 are likely mediated through attenuation of the overactivated p38-mitogen-activated protein kinase signaling pathway [35].

More definitive proofs for the direct contribution of the CB1 receptor to DN arose independently from murine models for type 1 and type 2 DM. In the first model induced
by streptozotocin (STZ), kidney expression of the CB₁ receptor is enhanced in both diabetic mice [33] and rats [37]. More specifically, colocalization of the CB₁ receptor with nephrin points to their predominant expression in podocytes. Moreover, pharmacological inhibition of the CB₁ receptor by AM251 ameliorates STZ-induced albuminuria and prevents the downregulation of podocyte proteins implicated in the maintenance of glomerular permselectivity to proteins [33]. Because proteinuria is an independent predictor of renal outcome in patients with type 1 DM [64], a recent study tested the specific role of CB₁ receptors in mediating urinary protein excretion. Using a genetic CB₁ activation mouse model and pharmacological stimulation of CB₁ in rats, Hsu et al. [65] showed that CB₁ receptor activation/stimulation increases urinary protein levels and is associated with enhanced glomerular CB₁ and vascular endothelial growth factor (VEGF) expression levels, as well as a subsequent reduction in nephrin gene and protein expression levels, suggesting a CB₁/VEGF-dependent signaling pathway that may lead to podocyte dysfunction and proteinuria.

Considering that type 2 DM may also lead to renal dysfunction, a study by Buraczynska et al. [66] recently reported a significant association between a CB₁ receptor gene polymorphism (G1359A) and DN in patients with type 2 DM. To date, two murine models for type 2 DM have been utilized to test the involvement of CB₁ receptors in mediating urinary protein excretion. Using the diabetic db/db mouse model, Nam et al. [43] documented preferentially increased CB₁ receptor expression in glomerular podocytes and demonstrated that SR141716 treatment significantly inhibits the expression of profibrotic and proinflammatory molecules in the diabetic kidney. Insights into the mechanism by which the CB₁ receptor modulates podocyte injury in type 2 DM were found in a recent report by Jourdan et al. [41], who used the well-established Zucker diabetic fatty (ZDF) rat model. Chronic (3 months) in vivo treatment of ZDF rats with the novel peripherally restricted CB₁ receptor antagonist, JD5037 [48], completely prevents renal pathologies related to glomerular dysfunction, which are strongly correlated with the specific expression of CB₁ receptors in podocytes and the expression of renal oxidative/nitrative stress markers [41]. These findings highlight the therapeutic potential of such peripheral compounds in DN, especially since the development and clinical testing of globally acting CB₁ receptor antagonists such as SR141716 has been halted due to neuropsychiatric side effects [67].

Additional mechanistic insights into how CB₁ receptor activation influences DN is provided by in vitro studies testing the effects of high glucose (HG), high albumin (HA), and increased palmitic acid (PA) levels on different types of kidney cells including podocytes, proximal tubular cells, and mesangial cells. Several lines of evidence show that HG stimulation of podocytes significantly increases CB₁ receptor expression [41, 43, 45]. This elevation is associated with increased expression of collagen type IV, plasminogen activator inhibitor-1, and sterol regulatory element-binding transcription factor-1, and all of these effects are completely blocked by SR141716 and siRNA for the CB₁ receptor [43]. The relationship between the effect of HG and CB₁ receptor stimulation in podocytes has been tested by exposing cells to either 30 mM glucose or 5 μM arachidonyl-2′-chloroethylamide (a CB₁ receptor agonist). Both stimuli increase CB₁ receptor expression and decrease podocin and nephrin expressions, effects that are prevented by JD5037 and siRNA-mediated knockdown of podocyte CB₁ receptor [41]. Likewise, downregulation of podocyte CB₁ receptor expression or pharmacological blockade by AM251 prevents HG-induced Akt phosphorylation, endoplasmic reticulum (ER) stress-related protein expression, and phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [45]. Moreover, a recent study suggests that HG-induced podocyte injury is mediated by a coactivator-associated arginine methyltransferase 1-AMP-activated protein kinase alpha and the CB₁ receptor signaling pathway [46]. Taken together, these findings highlight the significant role of the CB₁ receptor in mediating HG-induced podocyte dysfunction.

Other factors besides HG may affect podocyte function and lead to DN, one of which is the renin-angiotensin system [68]. Indeed, its important role in regulating CB₁ receptor-induced DN is supported by recent findings that angiotensin II, acting via the type 1 angiotensin II receptor, induces increased CB₁ receptor signaling in podocytes, an effect that is completely reversed by treatment with the angiotensin II receptor antagonist losartan [41]. Given evidence for CB₁ receptor and type 1 angiotensin II receptor heterodimerization, which amplifies the activity of the latter receptor [69], the proposed mechanism could provide novel insight into the pathologic pathways governing DN development in non-moglycemic conditions.

The effects of HG and HA were recently tested in another cell type within the kidney, the proximal tubules. In this work, Jenkin et al. [37] demonstrated that while HG alone does not affect CB₁ receptor expression, combined HG and HA treatment of HK2 proximal tubule cells significantly increases its expression. The functional role of CB₁ receptors within these cells is further demonstrated by findings that CB₁ receptor activation with AEA leads to hypertrophy, while its blockade with AM251 in the presence
of AEA reduces this effect in HK2 cells [34]. An important modifier of renal tubular damage in DN is elevated levels of PA, which is known to activate inflammatory, ER stress, and apoptosis pathways in renal proximal tubule cells [70, 71]. In fact, PA upregulates CB1 receptor mRNA and protein expression and promotes the receptors internalization in these cells. Furthermore, PA-induced activation of CB1 receptor decreases cell proliferation and induces apoptosis by inducing the ER stress response, effects that are completely antagonized by either pharmacological blockade of CB1 receptor or siRNA knockdown [47].

A similar observation for increased CB1 receptor expression and its cellular internalization was recently reported in primary rat mesangial cells exposed to HG conditions [50]. The effect of HG on these cells induces apoptosis via NF-κB and phospholipase A2 stimulation, which, in turn, reduces expression of the ER stress chaperone GRP78 and increases levels of p-PERK, p-eIF2α, pAFT4, and CHOP [50]. These ER stress proteins have been also linked to DN development in vivo [72]. A parallel signaling pathway via Ras, ERK, and peroxisome proliferator-activated receptor gamma was recently suggested to modulate the HG-induced CB1 receptor-mediated inflammation and fibrosis in mesangial cells [42].

The specific role of the CB1 receptor in the development of renal fibrosis was recently demonstrated in several human nephropathies and mice subjected to unilateral ureteral obstruction (UUO) [38]. In this mouse model, the CB1 receptor was among the most significantly upregulated genes, especially in renal tubules and podocytes and also in interstitial myofibroblasts. High CB1 receptor expression is also found in human nephropathies and correlates with kidney function. Moreover, genetic inactivation and pharmacological blockade by either globally acting or peripherally restricted CB1 receptor antagonists dramatically ameliorates the development of renal fibrosis in mice during UUO [38]. This suggests that the CB1 receptor plays an important role in renal fibrosis regardless of the initial renal injury.

Role of CB2 receptor in DN

Unlike CB1, several lines of evidence show that the CB2 receptor has a protective role in the diabetic kidney. Increased hypertrophy is observed in renal proximal tubule cells treated with the CB2 inverse agonist AM630 [34]. In the same cells, reduced mRNA and protein levels of CB2 receptor are measured following exposure to HA in the presence and absence of HG. These changes are likely mediated by internalization of albumin and are not regulated by ERK1/2 signaling [52]. While CB2 receptor expression is unaffected in STZ-induced diabetic mice and rats [51, 52], its glomerular expression is downregulated in patients with advanced DN [51]. This observation could be explained by increased intraglomerular pressure, but not renal hyperglycemia. Indeed, one study showed a substantial reduction in CB2 receptor expression following exposure of cultured podocytes to mechanical stretch but not an HG milieu [73]. Chronic treatment of STZ-induced diabetic mice with the selective CB2 agonist AM1241 ameliorates albuminuria and nephrin and zonula occludens mRNA downregulation. Yet it does not affect glomerular hyper trophy or monocyte chemotactic protein 1 expression [51]. Likewise, CB2 receptor deletion in STZ-treated mice exacerbates albuminuria, renal function, nephrin and podocin protein loss, and mesangial expansion [73]. Unlike a previous study by the same group, global deletion but not pharmacological CB2 receptor activation regulates renal fibrosis. In their earlier study, Barutta et al. [51] demonstrated that AM1241 does not ameliorate renal fibrosis, while their recent findings show that the expressions of fibronectin, type I collagen, and type IV α4 chain collagen are further enhanced in CB2-null diabetic mice [73], suggesting that pharmacological modulation of CB2 receptor by AM1241 is not sufficient to protect against renal fibrosis.

To clarify how monocyte infiltration could be a potential mediator in the genetic absence of CB2 receptor and indirectly affects kidney function by releasing cytokines and reactive oxygen species (ROS), it is found that transplantation of CB2-null bone marrow cells does not magnify albuminuria, renal dysfunction, and/or fibrosis in STZ-treated wild-type animals [73].

In a similar in vivo mouse model of nephropathy, Mukhopadhyay et al. [74] found that treatment of mice with the CB2 receptor agonist HU-308 attenuates cisplatin-induced DN, which is associated with increased chemokine production, inflammatory cell infiltration in the kidney, and the consequent release of ROS and inflammatory mediators that lead to tubular cell apoptosis [74]. In a follow-up study, Horváth et al. [75] tested the therapeutic effect of (E)-β-caryophyllene (BCP) in cisplatin-induced DN. BCP, which is a compound found in many essential oils of spices and a natural CB2 agonist [76], can markedly attenuate cisplatin-induced decline in kidney function and ameliorate the observed histological damage. Its protective effect is completely abolished in CB2 receptor knockout mice, demonstrating that it is mediated through CB2 receptors. Taken together, these preclinical findings suggest that targeting CB2 cannabinoid receptors may represent a novel protective strategy against DN.
**eCBs and obesity-related kidney dysfunction**

Recently, increasing attention has been paid to obesity-associated renal structural and functional changes that develop early in the course of obesity and metabolic syndrome [77–79]. In fact, obese individuals have a threefold greater risk of developing end-stage renal disease (ESRD) than non-obese individuals [80]. Even in the absence of DM and hypertension, which account for >70% of ESRD [81, 82], obesity induces hemodynamic and morphological changes in the kidney (e.g. glomerular hypertrophy, glomerular basement membrane thickening, mesangial matrix expansion, and increased tubular inflammation) [83, 84]. Together with renal inflammation [85] and oxidative stress [86], these changes may lead to decreased renal function and ultimately glomerulosclerosis and tubulointerstitial fibrosis [78, 87–89].

Several lines of evidence indicate that overstimulation of the eCB system via the CB1 receptor contributes to the pathogeneses of obesity and metabolic syndrome. By activating CB1 receptors in the brain, eCBs produce marijuana-like effects including an increase in appetite (the “munchies”) and lipogenesis [90, 91]. CB1 receptor-null mice are resistant to diet-induced obesity (DIO), hepatic steatosis, and the associated hormonal/metabolic changes, even though their caloric intake is similar to that of wild-type mice [11, 92]. As the kidney is a major source of eCBs and contains the CB1 receptor, the possible role of the eCB system in regulating obesity-related kidney dysfunction has been explored in several studies. Long-term treatment of obese *fa/za* Zucker rats (a strain that is characterized by hyperphagia and obesity due to a mutation in the leptin receptor-encoding gene) with the CB1 receptor antagonist SR141716 significantly delays the development of proteinuria, improves creatinine clearance, and decreases the severities of glomerular and tubulointerstitial lesions and renal hypertension [40]. Measurements of kidney eCB levels in DIO mice reveals a significant increase in AEA levels, which could suggest an elevated eCB “tone” that may directly affect renal function via the CB1 receptor [58]. Likewise, increased CB1 receptor expression was found in DIO rats, and chronic blockade of CB1 receptors by AM251 reverses obesity-induced tubular hypertrophy, albuminuria, and plasma creatinine levels [36].

A major feature of DIO is leptin resistance, probably induced by hyperleptinemia [93] due to increased leptin production by adipocytes and its reduced clearance by the kidney. The latter mechanism involves the renal proximal tubule cells, in which leptin is metabolically degraded following its uptake by the multifunctional endocytic receptor megalin [94]. In a recent study, the CB1 receptor was shown to regulate megalin expression and leptin uptake and degradation. First, the renal megalin expression is reduced by obesity in wild-type but not CB1 receptor-null mice, and peripherally restricted CB1 receptor blockade by JD5037 reverses the obesity-induced decline in megalin mRNA and protein expression levels in DIO mice. Second, blockade of CB1 receptor in cultured renal proximal tubule cells increases megalin expression and leptin uptake and degradation [48]. Because megalin mediates albumin uptake in renal proximal tubule cells [95], impaired megalin expression and/or activity may result in albuminuria. In accordance with the in vivo study published by Tam et al. [48], recent findings demonstrate that elevated leptin levels, which regulate transforming growth factor-beta expression in the renal proximal tubule cells, reduce albumin handling by these cells via altered megalin expression and function [96]. On the other hand, the same group reported increased megalin expression in a DIO rat model and no significant alteration in its expression levels following AM251 treatment [36], suggesting that other mechanisms (e.g. hyperglycemia) might contribute to the regulation of megalin. Collectively, these findings highlight the therapeutic potential of targeting the CB1 receptor in obesity-induced renal dysfunction.

As per the role of the CB1 receptor in this phenomenon, recent work by Jenkin et al. [53] determined the renal effect of CB2 receptor agonism and antagonism in DIO rats. Stimulation of CB2 receptors with AM1241 ameliorates the progression of obesity-related kidney dysfunction as measured by urinary protein and renal sodium excretion rates, while antagonism of CB1 receptors with AM630 reduces creatinine clearance, indicating enhanced renal failure.

**Concluding remarks**

The eCB system is present in the kidney where it is involved in controlling various renal functions with important therapeutic implications. Increased CB1 receptor activity contributes to kidney hemodynamic abnormalities and dysfunction, whereas CB2 receptor blockade may attenuate and delay these changes. eCBs acting via CB1 receptors in podocytes, proximal tubule cells, and mesangial cells have emerged as mediators of both DN and obesity-associated renal dysfunction. This provides strong...
evidence for the therapeutic use of CB1 receptor antagonists in these conditions. Although adverse neurophysi- 
sic effects limit the therapeutic potential of centrally 
acting CB1 receptor antagonists, the recent development of second-generation, peripherally restricted CB1 receptor 
antagonists may alleviate these problems. Additionally, 
non-psychoactive CB2 receptor agonists may offer thera-
peutic benefit in attenuating kidney injury and promoting 
tissue repair in DN- and obesity-induced renal damage.

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