The role of cannabinoid signaling in acute and chronic kidney diseases

Federica Barutta[1], Graziella Bruno[1], Raffaella Mastrocola[2], Stefania Bellini[1] and Gabriella Gruden[1]

[1]*Laboratory of Diabetic Nephropathy, Department of Medical Sciences, University of Turin, Turin, Italy; and* [2]*Department of Clinical and Biological Sciences, University of Turin, Turin, Italy*

The endogenous cannabinoids anandamide and 2-arachidonoylglycerol bind to the cannabinoid receptors of type 1 and 2. These receptors are also the binding sites for exogenous, both natural and synthetic, cannabinoids that are used for recreation purposes. Until recently, cannabinoids and cannabinoid receptors have attracted little interest among nephrologists; however, a full endocannabinoid system (ECS) is present in the kidney and it has recently emerged as an important player in the pathogenesis of diabetic nephropathy, drug nephrotoxicity, and progressive chronic kidney disease. This newly established role of the ECS in the kidney might have therapeutic relevance, as pharmacological modulation of the ECS has renoprotective effects in experimental animals, raising hope for future potential applications in humans. In addition, over the last years, there has been a number of reported cases of acute kidney injury (AKI) associated with the use of synthetic cannabinoids that appear to have higher potency and rate of toxicity than natural *Cannabis*. This poorly recognized cause of renal injury should be considered in the differential diagnosis of AKI, particularly in young people. In this review we provide an overview of preclinical evidence indicating a role of the ECS in renal disease and discuss potential future therapeutic applications. Moreover, we give a critical update of synthetic cannabinoid-induced AKI.

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Correspondence: *Gabriella Gruden, Diabetic Nephropathy Laboratory, Department of Medical Sciences, University of Turin, C/so Dogliotti 14, 10126, Turin, Italy. E-mail: gabriella.gruden@unito.it*

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Chronic kidney disease (CKD) is the common end point of renal diseases of multiple etiologies, including diabetic kidney disease (DKD), obesity-associated kidney disease, chronic tubulointerstitial damage, and repeated acute kidney disease (AKI). Podocyte damage causes the development of proteinuria, which is a major predictor of renal function decline. Renal fibrosis together with a low-grade inflammation underlies the progression of CKD to end-stage renal disease.

Despite our increasing understanding of these processes, therapeutic strategies to effectively contrast both onset and progression of these abnormalities are still insufficient. Preclinical data suggesting an important role of the endocannabinoid system (ECS) in governing these processes points to the cannabinoid receptors as potential novel targets for treatment.

CANNABINOIDS AND CANNABINOID RECEPTORS

Cannabinoids

The recreational effects of *Cannabis sativa* have been known for thousands of years. However, it was only in the 1960s that Δ9-tetrahydrocannabinol (Δ9-THC) was identified as the major psychoactive component. This landmark discovery led to the identification of the endogenous Δ9-THC binding sites that were cloned in the 1990s and named cannabinoid receptor types 1 and 2 (CB1R and CB2R)[1].

The existence of specific receptors for cannabis-derived molecules in mammalian cells prompted the search for their endogenous ligands. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) were recognized as the major CB1R and CB2R ligands, with CB1R favoring binding to AEA. These compounds are synthetized "on demand" from lipid precursors, act locally in an autocrine or paracrine manner, and are then rapidly degraded.[1]

Synthetic cannabinoids (SCBs) were generated as a research tool to clarify cannabinoid biochemistry, but since the 2000s psychoactive SCBs have emerged in the recreational drug market as a less expensive and more potent alternative to *Cannabis*.

Cannabinoid receptors

The cannabinoid receptors CB1R and CB2R are coupled through $G_{i/o}$ proteins, negatively to adenylate cyclase and positively to mitogen-activated protein kinases, and can also modulate ion channels. In addition, CB1R can activate adenylate cyclase through G_s proteins and increase intracellular

calcium through $G_{q/11}$ proteins[2,3] (Figure 1). CB1Rs are highly expressed at central and peripheral nerve terminals, where they inhibit neurotransmitter release, while CB2R are present predominantly on inflammatory cells, where they exert anti-inflammatory effects, including inhibition of cytokine release. Therefore, both CB1R and CB2R suppress the release of chemical messengers.[1]

Evidence that CB1Rs also play an important role in the periphery has clearly emerged from studies on obesity, showing that the CB1R antagonist rimonabant reduces body weight by acting predominantly on peripheral CB1R rather than on central neurons. This line of research has led to the discovery that peripheral CB1R promotes energy storage and affects both lipid metabolism and insulin sensitivity, significantly contributing to the pathogenesis of obesity, metabolic syndrome, and type 2 diabetes mellitus.[4] Although rimonabant was proven effective in human clinical trials and approved for the treatment of obesity in several countries, it was then withdrawn from the market because of important adverse central effects. However, research on the role of CB1R in the periphery continued and has recently received new inspiration with the development of second-generation CB1R antagonists that poorly cross the blood-brain barrier. These "peripheral restricted" CB1R blockers retain the peripheral beneficial effects of global CB1R antagonists and are thus promising novel therapeutic tools.[4–7]

Today we know that CB1R and CB2R are present in a vast array of cells and are important in a multitude of pathophysiological conditions, including cancer, cardiovascular, respiratory, dermatologic, and liver diseases.[8] It is also increasingly recognized that CB1R and CB2R are often co-expressed on either the same cell or neighboring cells, causing opposite effects in a "yin-yang" relationship. Signaling though CB2R on either inflammatory or parenchymal cells has anti-inflammatory effects and lowers inflammation-driven fibrosis, while signaling through CB1R promotes oxidative stress and inflammation, resulting in both cell apoptosis and fibrosis (Figure 2).

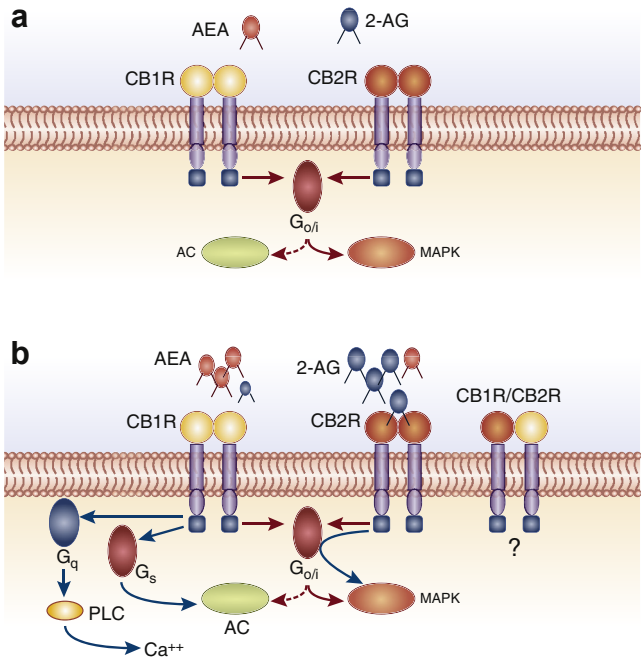

Figure 1 | Cannabinoid receptor types 1 and 2 (CB1R and CB2R) ligands and signaling pathways. (**a**) CB1R and CB2R share ligands (AEA, 2-AG) and signaling pathways because they are both coupled through $G_{i/o}$ proteins, negatively to adenylate cyclase (AC) and positively to mitogen-activated protein kinases (MAPK). (**b**) Additional factors possibly explaining the opposing CB1R and CB2R effects: CB1R binds predominantly to AEA, whereas CB2R favors 2-AG. CB1R also activates AC through G_S proteins and phospholipase C (PLC) though G_q, the latter leading to enhanced intracellular calcium. Coupling of CB2R to AC inhibition is influenced by CB2R expression levels, surrounding conditions, and engaging ligand. 2-AG displays functional selectivity, potently activating MAPK while inhibiting AC exclusively at high concentrations. The formation of CB1R/CB2R heterodimers with unclear pharmacology adds further complexity.

THE ECS IN THE KIDNEY

The ECS in the normal kidney

Both CB1R and CB2R are present in the normal kidney as detailed in Figure 3, though their expression is very low except for CB2R within the glomeruli. Moreover, renal tissue is enriched with endocannabinoids, implying physiological relevance. The role of the ECS in the normal kidney remains poorly understood; however, AEA infusion decreases glomerular filtration rate and increases renal blood flow, independent of changes to blood pressure, and *in vitro* AEA vasodilates arterioles in a CB1R-dependent manner. Therefore, the ECS is likely involved in the regulation of renal blood flow and may also play a role in sodium reabsorption at the tubular level.[9]

The ECS in models of kidney diseases

Early studies have explored the possibility that the beneficial effects of CB1R blockade on metabolism would result in

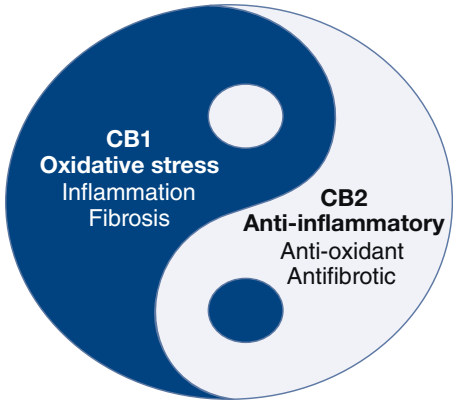

Figure 2 | The endocannabinoid receptors exhibit a "yin-yang" relationship. Activation of the cannabinoid type 1 (CB1) receptor enhances oxidative stress, inflammation and fibrosis, whereas signaling through the cannabinoid type 2 (CB2) receptor has opposite anti-inflammatory, anti-oxidative, and antifibrotic effects.