Chapter-2

Review of Literature
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Deutsch et al., 1997 reported that anandamide was expressed in kidney homogenates, cultured renal endothelial cells (EC), and mesangial cells. Further these cells also contain anandamide amidase. Moreover, reverse-transcriptase PCR showed that EC contain transcripts of cannabinoid type 1 (CB1) receptors, while mesangial cells have mRNA of both CB1 and CB2 receptors. In addition, Anandamide (1μM) vasodilated juxtamedullary afferent arterioles, which were perfused in vitro and this vasodilation was blocked by nitric oxide (NO) synthase inhibition with L-NAME (0.1 mM) or CB1 receptor antagonism with SR141716A (1μM). Furthermore, Anandamide (10 nM) stimulated CB1-receptor-mediated NO release from perfused renal arterial segments. Finally, anandamide (1μM) produced a NO-mediated inhibition of KCl-stimulated [3H] norepinephrine released from sympathetic nerves on isolated renal arterial segments. Concluding that anandamide signaling system was present in the kidney, where it exerts significant vasorelaxant and neuromodulatory effects. (Deutsch et al., 1997).

Obese Zucker rats treated with rimonabant showed significant reduction in obesity along with a sustained decrease in body weight, transient reduction in food intake and an increase in plasma adiponectin and was also associated with significant reduction in plasma total cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, triglycerides, glucose, norepinephrine, plasminogen activator inhibitor 1, and preservation of pancreatic weight and beta-cell mass index. The cannabinoid antagonist also attenuated the increase in proteinuria, urinary N-acetylglucosaminidase excretion, plasma creatinine, and urea nitrogen levels with improvement of creatinine clearance. Renal hypertrophy along with glomerular and tubulointerstitial lesions were also
reduced by rimonabant treatment (a specific CB1 receptor antagonist) with no alterations in the hemodynamics. The study suggested that rimonabant preserved renal function and increased the survival (Janaik et al., 2007).

Larrinaga et al., 2010 performed RT-PCR, western-blot and immunohistochemical assays on adult and fetal kidneys. The RT-PCR confirmed the presence of CB1 receptor mRNA and the absence of the CB2 receptor mRNA in adult and fetal kidney. Further, Western-blot and immunohistochemical assays also revealed the presence of the CB1 cannabinoid receptor protein, which displayed a similar distribution in fetal and adult kidneys. Finally the study suggested that endocannabinoid system was involved in the physiology and development of human kidney (Larrinaga et al., 2010).

Jenkin et al., 2010 investigated the role of cannabinoid receptors in human proximal tubular cells (HK2). Characterisation of HK2 cells demonstrated that mRNA and protein for CB1, CB2, TRPV1 and GPR55 occurs in these cells. Further, activation of the cannabinoid receptors with anandamide significantly increased hypertrophy in HK2 cells. In addition, treatment with CB1 antagonist AM-251, reduced hypertrophy while treatment with CB2 (AM-630) and TRPV1 (SB-366791) antagonists increased hypertrophy in the HK2 cells. The results indicated that in human proximal tubule, these receptors regulate cellular function by activating different cell signalling pathways and use of the cannabinoid agents may be beneficial therapeutic target in the treatment of diseases such as diabetes and obesity.

Mukhopadhyay et al., 2010; Cisplatin significantly increased endocannabinoid anandamide content, activated p38 and JNK mitogen-activated protein kinases (MAPKs), apoptotic and poly (ADP-ribose) polymerase-
dependent cell death, enhanced inflammation (leucocyte infiltration, tumour necrosis factor-a and interleukin-1b) and promoted oxidative/nitrosative stress [increased expressions of superoxide-generating enzymes (NOX2(gp91phox), NOX4), inducible nitric oxide synthase and tissue 4-hydroxynonenal and nitrotyrosine levels] in the kidneys of mice which were accompanied by marked histopathological damage and impaired renal function. Pharmacological inhibition of CB1 receptors with AM281 or SR141716 markedly attenuated the cisplatin-induced renal dysfunction by ameliorating the increased endocannabinoid anandamide content, activated the p38 and JNK mitogen-activated protein kinases, cell death and inflammatory response. The results suggested that endocannabinoid system through CB1 receptors promotes cisplatin-induced tissue injury by amplifying MAPK activation, cell death and interrelated inflammation and oxidative/nitrosative stress. The study reported that blockade of CB1 receptors may exert beneficial effects in renal diseases associated with enhanced inflammation, oxidative/nitrosative stress and cell death.

Barutta et al., 2010; In diabetic mice the CB1 receptor were overexpressed within the glomeruli, predominantly by glomerular podocytes. Also the diabetic mice showed increased albuminuria as compared to that of normal control. Blockade of CB1 receptors by AM251 ameliorated diabetes-induced albuminuria. Furthermore, CB1 blockade completely prevented diabetes-induced downregulation of nephrin, podocin, and ZO-1. The study revealed that in experimental type 1 diabetes the CB1 receptors were overexpressed on the glomerular podocytes and blockade of the CB1 receptor ameliorated albuminuria possibly via prevention of nephrin, podocin, and ZO-1 loss.
Lim et al., 2011 investigated the effects of high glucose (HG) on CB1 receptor expression and its signaling pathways in primary cultured rat mesangial cells. HG significantly increased CB1 receptor mRNA and protein levels in a time-dependent manner and also induced CB1 receptor internalization. Further, nuclear factors such as NF-kB and Phospholipase A2 (PLA2) were involved in the high glucose induced increase in CB1 receptor levels. Furthermore, high glucose inhibited the expression of GRP78, and induced increase in endoplasmic reticulum stress proteins, including p-PERK, p-eIF2α, p-ATF4, and CHOP. In addition, high glucose increased the Bax/Bcl-2 ratio and increased the amounts of cleaved PARP and caspase-3. Suggesting that CB1 receptors mediates high glucose induced apoptosis via endoplasmic reticulum stress in cultured rat mesangial cells. The study also proved that blockade of CB1 receptors by CB1 specific receptor antagonist AM251 attenuated the high glucose induced apoptotic effect by attenuating the levels of Bax/Bcl-2 ratio, cleaved PARP and caspase-3. Also, AM251 also downregulated the elevated levels CB1 receptors. The study suggested that blockade of CB1 receptors may be a potential therapeutic target in diabetic nephropathy.

Nam et al., 2012, examined the effect of the cannabinoid (CB)1 receptor antagonist, SR141716, on insulin resistance and diabetic nephropathy in db/db mice. The db/db mice were treated with the CB1-specific antagonist SR141716. Treatment with SR141716 significantly improved insulin resistance and lipid abnormalities. Concomitantly, CB1 antagonism improved cardiac functional and morphological abnormality, hepatic steatosis, and phenotypic changes of adipocytes into small differentiated forms, associated with increased adiponectin expression and decreased lipid hydroperoxide levels. CB1 receptor was
overexpressed in diabetic kidneys, especially in podocytes. Treatment with the SR141716 markedly decreased urinary albumin excretion and mesangial expansion and suppressed profibrotic and proinflammatory cytokine synthesis. Furthermore, SR141716 improved renal lipid metabolism and decreased urinary 8-isoprostane levels, renal lipid hydroperoxide content, and renal lipid content. In cultured podocytes, high-glucose stimulation increased CB1 receptor expression, and SR141716 treatment abolished high-glucose-induced up-regulation of collagen and plasminogen activator inhibitor-1 synthesis. Additionally, knockdown of CB1 receptor expression by stealth small interfering RNA abolished high-glucose-induced sterol-regulatory element-binding protein-1 (SREBP-1) expression in podocytes. From the results obtained the study suggested that CB1 blockade improves insulin resistance and protect against renal injury through both metabolic and antifibrotic effects in type 2 diabetic nephropathy. Targeting CB1 blockade could therefore provide a new therapeutic target to prevent type 2 diabetic nephropathy.

Lim and Park, 2012, examined renal kallikrein-kinin system (KKS), apoptosis and its related signaling pathway in rat podocytes. In addition, they studied the relationship of cannabinoid CB1 receptors with high glucose and BK receptors. High glucose (25 mM) treatment decreased cell viability and increased DNA fragmentation. Also, high glucose-induced DNA fragmentation and PARP and caspase-3 activation were blocked by both [des-Arg(10)]-HOE 140 (a B1R antagonist) and HOE 140 (a B2R antagonist). High glucose also has increased Akt phosphorylation, ER stress-related protein expression, and NF-κB/IκB phosphorylation in podocytes, which were blocked by both [des-Arg(10)]-HOE 140 and HOE 140. In addition, B1R and B2R siRNA transfections prevented high
glucose-induced Akt and NF-κB activations in rat podocytes. Moreover, AM251 (a CB1 receptor antagonist) treatment and CB1 receptor siRNA transfection blocked the high glucose-induced stimulation of BK receptor expression, Akt activation, and NF-κB activation. The suggested that hyperglycemia induces apoptosis via the stimulation of B1R and B2R expression through CB1 receptor activation in rat podocytes in vitro, which is associated with the development of diabetic nephropathy.

Barutta et al., 2011, the expression of CB2 receptors was studied in kidney biopsies from patients with advanced DN, in early experimental diabetes, and in cultured podocytes. Further the levels of endocannabinoids and related enzymes were measured in the renal cortex from diabetic mice. In addition, the functional role of CB2 receptors was also assessed. The podocytes expressed the CB2 receptor both in vitro and in vivo. Further, CB2 expression was downregulated in kidney biopsies from patients with advanced DN, and renal levels of the CB2 ligand 2-arachidonoylglycerol were reduced in diabetic mice, suggesting impaired CB2 regulation. Moreover, In experimental diabetes, AM1241 ameliorated albuminuria, podocyte protein downregulation, and glomerular monocyte infiltration, without affecting early markers of fibrosis. In addition, AM1241 (a specific CB2 receptor agonist) reduced CCR2 expression in both renal cortex and cultured podocytes, suggesting that CB2 activation may interfere with the deleterious effects of MCP-1 signalling. This experimental study suggested that CB2 receptors are expressed by cultured podocytes, and in experimental diabetes. Further, CB2 activation ameliorates both albuminuria and podocyte protein loss, suggesting a protective effect of signaling through CB2 in DN.
Bibliography


