CANNABIDIOL AND DIABETES

Diabetes 1 / Diabetes 2 – The Remarkable Impact of CBD Treatments

Diabetes is an autoimmune disease; a problem within the body that causes blood glucose (sugar) levels to rise higher than normal. The American Diabetes Association describes Type 1 diabetes as the body's inability to produce insulin. Insulin is a hormone that is needed to convert sugar, starches, and other food into the energy that is required for daily life. Type 2 diabetes is defined as the body's inability to use insulin properly, referred to as insulin resistance. At first, the pancreas makes extra insulin to compensate for the initial deficit. Eventually, the onset of insulin deficiency occurs when the pancreas can no longer keep up; no longer able to keep blood glucose at normal levels.

Type 1 diabetes (formerly called juvenile-onset or insulin-dependent diabetes); affects 5% of people with diabetes have this form of the disease. Type 1 diabetes is usually diagnosed in children and young adults.

Type 2 diabetes (formerly called adult-onset or non–insulin-dependent diabetes) can develop at any age. It most commonly develops during adulthood although it is rising in children. Type 2 diabetes accounts for the vast majority of people who have diabetes—90 to 95 out of 100 people.

Specifically, our immune system attacks the cells in the pancreas (Beta Cells in the Islets of Langerhans), which produce insulin. By definition, islets are actually clusters of cells; each "islet" containing 3,000 to 4,000 cells. Scientists estimate there are 1 million islets in a healthy, adult pancreas accounting for 1 to 2% of the entire organ. Within each islet there are several types of cells working together to regulate blood sugar. When these beta cells are destroyed, the sugar we consume is no longer delivered to the cells in our body but instead over burdens the blood plasma. As a result, the high blood sugar compromises proteins throughout the body (a process referred to as glycation,) which is magnified further by oxidative stress (inflammation that damages arteries throughout the body.) These processes contribute to the onset of diabetes type 2 and a multitude of serious complications, i.e., heart and blood vessel disease, nerve damage, kidney damage, eye damage possibly leading to blindness, foot, skin and mouth infections, hearing issues, pregnancy complications, and osteoporosis.

Research shows that plant cannabinoids have an immune tempering effect on the TH-1 lymphocyte, a type of immune cell responsible for the destruction of the beta cells while simultaneously causing the more beneficial helper and anti-

inflammatory immune cell TH-2, to positively alter the size of the beta cell toward growth. CBD can create endogenous precursor cells in the pancreas to slowly give rise to increased beta cell mass and volume in the early stages of Type 1 diabetes, thereby maintaining normal blood sugar levels. CBD has been shown to decrease the need for insulin in type 1 diabetes by a significant number - 58%. CBD has also successfully reversed type 2 diabetes; it causes glucose breakdown, lipid breakdown, and increases insulin sensitivity. According to Raphael Mechoulam, PhD., professor of Medical Chemistry and Natural Products, at Hebrew University in Jerusalem, and world renown for his expertise on the Cannabis Sativa plant, "CBD did not only prevent the onset (of diabetes), it blocked the development of diabetes." The significance of this is beyond measure for America is in the midst of a diabetes epidemic. Over the last 20 years, the number of adults diagnosed with diabetes has more than doubled; the number of children being diagnosed is alarming.

The Endocannabinoid System and Plant-Derived Cannabinoids in Diabetes and Diabetic Complications

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349875/

Diabetic Nephropathy

Diabetes is a leading cause of renal failure, accounting for 44% of all new cases in 2008. Hyperglycemia stimulates ROS generation, which ultimately leads (via diverse pathways) to diabetic nephropathy characterized by mesangial expansion, thickening of the glomerular basement membrane, and glomerular sclerosis. There is strong evidence that both the synthetic and degradative pathways of the ECS are present in the kidney, and the CB_1 receptor is expressed in both glomeruli and tubular epithelial cells.[72] In intrarenal arteries, the CB_1 receptor is present in the endothelium, and the CB_2 receptor is present in mesangial cells.[71] Cannabinoid receptors play opposing roles in the regulation of oxidative stress in the kidney, as observed in a murine nephropathy model induced by cisplatin. The CB_1 receptor promotes inflammation, oxidative/nitrative stress, and cell death through the activation of the p38-MAPK pathway. In contrast, CB_2 receptor agonists limit damage after cisplatin administration by reducing oxidative stress, inflammation, and apoptosis.[74] For therapeutic purposes, it is important that plant-derived CBD is also able to ameliorate cisplatin-induced nephrotoxicity.

Diabetic Retinopathy

Diabetes is the leading cause of new cases of blindness and preventable blindness among adults. Vascular inflammation and endothelial cell death caused by oxidative and nitrative stress are characteristics of diabetic retinopathy. In the early stages, retinopathy is characterized by microaneurysm

formation and microvascular lesions and later by extensive intraretinal hemorrhage that culminates in proliferative diabetic retinopathy with neovascularization and either preretinal or vitreous hemorrhage.

The ECS is present in the retina as shown by the presence of AEA, 2-AG, and the metabolizing enzymes FAAH and MAGL. CB_1 receptors are expressed in the layers of the retina, ciliary body, iris, and choroid, whereas CB_2 receptors are localized to the retina. It has been shown that EC levels are elevated in the eyes of patients with diabetic retinopathy. 2-AG levels are elevated in the iris, whereas AEA levels are increased in the cornea, ciliary body, retina, and the choroid. The role of such an increase gained importance when we received insight into the role of CB_1 receptor activation in diabetic retinopathy. Deletion of the CB_1 receptor or treatment with a CB_1 receptor antagonist prevented retinal cell death in a murine diabetes model. Treatment of diabetic mice or human retinal cells with CB_1 receptor antagonists after exposure to high glucose levels attenuated oxidative/nitrative stress, reduced NF-κB activation and adhesion molecule levels, and attenuated MAPK activation. These observations were supported by the fact that hyperglycemia up-regulated CB_1 receptor expression and induced apoptosis in retina pigment epithelial cells, effects that were preventable with a CB_1 receptor antagonist. Interestingly, hyperglycemia also decreased FAAH expression, leading to a locally increased concentration of AEA and thereby increasing apoptosis via CB_1 receptor signaling.

The effect of CBD was also examined in experimental diabetic retinopathy. CBD was able to reduce oxidative stress, inflammation, cell death, and vascular hyperpermeability associated with diabetes. Consistent with these findings, CBD also inhibited p38-MAPK signaling. Furthermore, CBD also attenuated high glucose–induced endothelial cell dysfunction, ROS generation, and barrier disruption in primary human coronary artery endothelial cells. The protective effects of CBD on retinal cell death were, at least in part, due to the reduction of tyrosine nitration of glutamine synthase in macroglial cells, thereby preventing the accumulation and excitotoxicity of glutamine through *N*-methyl-D-aspartate receptors.

Diabetic Neuropathy

Approximately 60% to 70% of people with diabetes have some kind of nervous system damage. The typical presentation is chronic, length-dependent sensorimotor neuropathy, which develops in a background of long-standing hyperglycemia and is associated with alterations of microvessels; it can be stabilized with rigorous glycemic control. Autonomic dysfunction and pain may develop over time as well.

CB_1 receptors are widely expressed throughout the central and peripheral nervous systems, whereas CB_2receptors are primarily restricted to the cells of the peripheral nervous system, microglia, and dorsal horn neurons. ECs are retrograde messengers with agonistic activity on presynaptic CB_1 receptors, slowing neurotransmission. A good example of this effect is the suppression of

nociceptive transmission in the periphery at the level of the posterior horn of the spinal cord. It has been proven that these peripheral CB_1 receptors play a key role in cannabinoid-induced analgesia. Interestingly, although CB_1 and CB_2agonists are effective in animal models of acute and chronic pain, in clinical trials, they only perform well in patients with chronic pain syndrome. Sativex spray containing THC and CBD is already approved for the treatment of pain in patients with multiple sclerosis and cancer pain unresponsive to opioid therapy in Canada, the United Kingdom, and Spain.

The first indication of the role of the ECS in diabetic neuropathy came from a murine diabetes model. A dual CB_1/CB_2 receptor agonist inhibited capsaicin-induced calcitonin gene–related peptide release, a measure of sensory neuron function, which was prevented by a CB_1 antagonist. AEA also inhibited capsaicin-induced calcitonin gene–related peptide release in a non-CB_1/CB_2 receptor–dependent fashion, which was interestingly lacking in diabetic mice. Mechanical allodynia in diabetic rats can also be attenuated by treatment with a nonselective cannabinoid agonist. A highly significant finding was that both CB_1 and CB_2 agonists demonstrated antinociceptive effects in mice with streptozotocin-induced diabetes, and there were no pronociceptive effects for either CB_1 or CB_2 antagonists. Even more promising is (in terms of developing and using CB_1 antagonists in the treatment of primary diabetes and diabetic complications) that subchronic CB_1 receptor antagonism has been shown to evoke a κ-opiate–dependent analgesia by increasing the transcription of genes encoding the opioid system in the spinal cord.

Both *in vitro* and *in vivo* findings regarding the role of cannabinoid receptors in the pathogenesis of diabetic peripheral neuropathy are contradictory. CB_1 receptor expression has been shown to be down-regulated in PC-12 cells exposed to high glucose levels and in dorsal root ganglia removed from diabetic rats; the synthetic cannabinoid HU-210 was able to restore impaired nerve growth factor–induced neurite outgrowth in cells exposed to high glucose levels in a CB_1 receptor–dependent manner, consistent with the earlier finding that HU-210 attenuates neural damage. *In vivo*, however, the CB_1 receptor antagonist RIO shows a beneficial effect in diabetic peripheral neuropathy. RIO improves decreased intraepidermal nerve fiber density and alleviates increased current perception threshold, which is closely associated with the attenuation of skin capillary loss, increase in blood flow, and reduction of TNF-α levels. RIO also ameliorates mechanical allodynia in diabetic mice, reduces oxidative stress in peripheral nerves, inhibits TNF-α overproduction in the spinal cord, and restores NGF content. The alleviation of mechanical allodynia with RIO was attributed to diminished sensitization of the transient receptor potential vanilloid receptor via CB_1 receptor antagonism.

In summary, CB_1 receptor antagonism appears to be a viable option for halting the progression of diabetic neuropathy and may provide some analgesic effects through a κ-opiate–dependent pathway. The natural cannabinoid CBD offers a further possible therapeutic advantage because it was able to attenuate the

development of neuropathic pain. This effect was associated with the restriction in the elevations of microglial density in the spinal cord and of phosphorylated p38-MAPK. The first clinical trial with Sativex has already been conducted in patients with painful diabetic neuropathy. Although the trial failed to show any advantage compared with placebo treatment, further analysis is needed because several confounding factors were present.

Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, inflammatory and cell death signaling pathways in diabetic cardiomyopathy

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Cannabidiol, a nonpsychoactive component of marijuana, has been shown to exert anti-inflammatory and antioxidant effects both *in vitro* and in various preclinical models of neurodegeneration and inflammatory disorders, independent from classical CB_1 and CB_2 receptors. Furthermore, CBD has recently been reported to lower the incidence of diabetes in non-obese diabetic mice and to preserve the blood-retinal barrier in experimental diabetes.
In the present study, we have evaluated the effects of CBD treatment (for 11 weeks administered after the destruction of pancreatic beta cells and development of frank type 1 diabetes, as well as in 8 weeks diabetic animals for 4 weeks) on myocardial dysfunction, inflammation, oxidative/nitrosative stress, cell death and interrelated signaling pathways, using a mouse model of type I diabetic cardiomyopathy or primary human cardiomyocytes exposed to high glucose. Since significant cardiac dysfunction in this model starts to develop from 4 weeks of established diabetes with gradually increasing fibrosis thereafter (peaking around 8 weeks of established diabetes), in the first treatment protocol we aimed to study if CBD treatment can prevent the development of characteristic alterations of type I diabetic cardiomyopathy, in the second if it is able to reverse these changes once they already developed.

A recent study has also suggested that the NF-κB activation may induce increased oxidative stress and contributes to mitochondrial and cardiac dysfunction in type II diabetes(9). Importantly, the oxidative-nitrosative stress, stress signaling and inflammatory pathways in diabetic cardiomyopathy are closely interrelated eventually promoting the development myocardial fibrosis.

CBD treatment (Suppl.Fig.1.) was able to attenuate the oxidative-nitrosative stress (decreased the myocardial ROS generation and expression of $p22^{phox}$, $p67^{phox}$, $gp91^{phox}$, restored glutathione content and SOD activity, decreased 3-NT formation) and alterations of the above mentioned pro-survival (Akt) and stress signaling (p38, p38α, JNK) pathways in diabetic hearts. It also attenuated the NF-

κB activation, expression of iNOS, TNFα, and ICAM-1, cell death and fibrosis in diabetic myocardium, and improved the associated characteristic functional alterations. Importantly, CBD treatment was able to attenuate/reverse (though to a lesser extent) some of the above mentioned diabetes-induced myocardial biochemical and functional changes following the establishment of diabetic cardiomyopathy with fibrosis. CBD also attenuated the high glucose-induced increased reactive oxygen and nitrogen species generation, NF-κB activation and cell death in primary human cardiomyocytes.

The above mentioned beneficial effects of CBD could be explained in part by its potent antioxidant properties, which was first suggested by the Nobel Prize winner Dr. Julius Axelrod. In Axelrod's study CBD was more protective against glutamateinduced neurotoxicity than any of the well-know antioxidants (e.g. ascorbate or α-tocopherol), indicating additional cytoprotective effects of CBD beyond its potent antioxidant properties. Indeed, our recent results suggest that CBD may exert potent effects on key pro-inflammatory pathways such as NF-κB and on pro-survival signaling such as Akt in vivo, which is most likely not related to its antioxidant effect. This is also supported by observations that CBD decreases inflammation in models in which conventional antioxidants are not very effective (e.g. in arthritis), as well as by recent studies demonstrating that CBD is a potent inhibitor of bacterial lipopolysaccharide-activated NF-κB proinflammatory pathway in microglia cells. These results are also in support of the emerging role of the inflammation in the development and progression of diabetic cardiomyopathy.

Collectively, our results strongly suggest that CBD may have tremendous therapeutic potential in the treatment of diabetic cardiovascular and other complications by attenuating diabetes-induced oxidative/nitrosative stress, inflammation, cell death and fibrotic pathways.

Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain

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Despite the frequency of diabetes mellitus and its relationship to diabetic peripheral neuropathy (DPN) and neuropathic pain (NeP), our understanding of underlying mechanisms leading to chronic pain in diabetes remains poor. Recent evidence has demonstated a prominent role of microglial cells in neuropathic pain states. One potential therapeutic option gaining clinical acceptance is the cannabinoids, for which cannabinoid receptors (CB) are expressed on neurons and microglia. We studied the accumulation and activation of spinal and thalamic microglia in streptozotocin (STZ)-diabetic CD1 mice and the impact of

cannabinoid receptor agonism/antagonism during the development of a chronic NeP state. We provided either intranasal or intraperitoneal cannabinoid agonists/antagonists at multiple doses both at the initiation of diabetes as well as after establishment of diabetes and its related NeP state.

Results

Tactile allodynia and thermal hypersensitivity were observed over 8 months in diabetic mice without intervention. Microglial density increases were seen in the dorsal spinal cord and in thalamic nuclei and were accompanied by elevation of phosphorylated p38 MAPK, a marker of microglial activation. When initiated coincidentally with diabetes, moderate-high doses of intranasal cannabidiol (cannaboid receptor 2 agonist) and intraperitoneal cannabidiol attenuated the development of an NeP state, even after their discontinuation and without modification of the diabetic state. Cannabidiol was also associated with restriction in elevation of microglial density in the dorsal spinal cord and elevation in phosphorylated p38 MAPK.

Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption

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In the present study, we have evaluated the effects of CBD, a nonpsychoactive component of marijuana, on HG-induced mitochondrial superoxide generation, NF-κB activation, iNOS expression, nitrotyrosine formation, upregulation of adhesion molecules ICAM-1 and VCAM-1, monocyte-endothelial adhesion, TEM of monocytes, and disruption of endothelial barrier function in HCAECs. We demonstrate that CBD attenuates HG-induced mitochondrial superoxide generation, NF-κB activation, nitrotyrosine formation, upregulation of iNOS and adhesion molecules ICAM-1 and VCAM-1, TEM of monocytes, monocyte-endothelial adhesion, and disruption of the endothelial barrier function in HCAECs by a mechanism independent from CB_1 and CB_2 receptors.

Consistently, CBD has been shown to exert anti-inflammatory and antioxidant effects both in vitro and in various preclinical models of neurodegeneration and inflammatory disorders, independent from classical CB_1 and CB_2 receptors. CBD is devoid of psychoactive effects due to a low affinity for the central nervous system CB_1 receptors and is well tolerated when chronically administered to humans. CBD has been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans since 2005. Furthermore, CBD has recently been reported to lower the incidence of diabetes in nonobese diabetic mice and to preserve the blood-retinal barrier in experimental diabetes.

Since reactive oxygen species/peroxynitrite/NF-κB pathway and downstream effectors, such as poly(ADP-ribose) polymerase-1, play important roles in the destruction of insulin-secreting pancreatic β-cells, it is conceivable that the above-mentioned anti-inflammatory effects of CBD could contribute to the recently observed antidiabetic effects in nonobese diabetic mice.

Collectively, our results suggest that the nonpsychoactive cannabinoid CBD have significant therapeutic benefits against diabetic complications and atherosclerosis by attenuating HG-induced mitochondrial superoxide generation, increased NF-κB activation, upregulation of iNOS and adhesion molecules, 3-NT formation, monocyte-endothelial adhesion, TEM of monocytes, and disruption of the endothelial barrier function. This is particularly encouraging in light of the excellent safety and tolerability profile of CBD in humans.

Cannabidiol lowers incidence of diabetes in non-obese diabetic mice

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Cannabidinoids are components of the Cannabis sativa (marijuana) plant that have been shown capable of suppressing inflammation and various aspects of cell-mediated immunity. Cannabidiol (CBD), a non-psychoactive cannabidinoid has been previously shown by us to suppress cell-mediated autoimmune joint destruction in an animal model of rheumatoid arthritis. We now report that CBD treatment significantly reduces the incidence of diabetes in NOD mice from an incidence of 86% in non-treated control mice to an incidence of 30% in CBD-treated mice. CBD treatment also resulted in the significant reduction of plasma levels of the pro-inflammatory cytokines, IFN-gamma and TNF-alpha. Th1-associated cytokine production of in vitro activated T-cells and peritoneal macrophages was also significantly reduced in CBD-treated mice, whereas production of the Th2-associated cytokines, IL-4 and IL-10, was increased when compared to untreated control mice. Histological examination of the pancreatic islets of CBD-treated mice revealed significantly reduced insulitis. Our results indicate that CBD can inhibit and delay destructive insulitis and inflammatory Th1-associated cytokine production in NOD mice resulting in a decreased incidence of diabetes possibly through an immunomodulatory mechanism shifting the immune response from Th1 to Th2 dominance.