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PRE-CLINICAL RESEARCH

Cannabidiol Attenuates Cardiac Dysfunction, Oxidative Stress, Fibrosis, and Inflammatory and Cell Death Signaling Pathways in Diabetic Cardiomyopathy

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Objectives: In this study, we have investigated the effects of cannabidiol (CBD) on myocardial dysfunction, inflammation, oxidative/nitrative stress, cell death, and interrelated signaling pathways, using a mouse model of type I diabetic cardiomyopathy and primary human cardiomyocytes exposed to high glucose.

Background: Cannabidiol, the most abundant nonpsychoactive constituent of Cannabis sativa (marijuana) plant, exerts anti-inflammatory effects in various disease models and alleviates pain and spasticity associated with multiple sclerosis in humans.

Methods: Left ventricular function was measured by the pressure-volume system. Oxidative stress, cell death, and fibrosis markers were evaluated by molecular biology/biochemical techniques, electron spin resonance spectroscopy, and flow cytometry.

Results: Diabetic cardiomyopathy was characterized by declined diastolic and systolic myocardial performance associated with increased oxidative-nitrative stress, nuclear factor- κ B and mitogen-activated protein kinase (c-Jun N-terminal kinase, p-38, p38 α) activation, enhanced expression of adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1), tumor

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necrosis factor- α , markers of fibrosis (transforming growth factor- β , connective tissue growth factor, fibronectin, collagen-1, matrix metalloproteinase-2 and -9), enhanced cell death (caspase 3/7 and poly[adenosine diphosphate-ribose] polymerase activity, chromatin fragmentation, and terminal deoxynucleotidyl transferase dUTP nick end labeling), and diminished Akt phosphorylation. Remarkably, CBD attenuated myocardial dysfunction, cardiac fibrosis, oxidative/nitrative stress, inflammation, cell death, and interrelated signaling pathways. Furthermore, CBD also attenuated the high glucose-induced increased reactive oxygen species generation, nuclear factor- κ B activation, and cell death in primary human cardiomyocytes.

Conclusions: Collectively, these results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications, and perhaps other cardiovascular disorders, by attenuating oxidative/nitrative stress, inflammation, cell death and fibrosis.

Key Words: cannabinoids • diabetic complications • inflammation • oxidative stress

Abbreviations and Acronyms

ADP = adenosine diphosphate
 CBD = cannabidiol
 HCM = human cardiomyocytes
 HG = high glucose
 HNE = hydroxynonenal
 ICAM = intercellular adhesion molecule
 I κ B- α = inhibitor of nuclear transcription factor nuclear factor- κ B
 iNOS = inducible nitric oxide synthase
 JNK = c-Jun N-terminal kinase
 MAPK = mitogen-activated protein kinase
 MMP = matrix metalloproteinase
 NADPH = nicotinamide adenine dinucleotide phosphate
 NF- κ B = nuclear factor kappa B
 NT = nitrotyrosine
 PARP = poly(ADP-ribose) polymerase
 ROS = reactive oxygen species
 SOD = superoxide dismutase
 THC = delta 9-tetrahydrocannabinol
 TNF = tumor necrosis factor
 TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling
 VCAM = vascular cell adhesion molecule

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