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Master Thesis Defense

Entitled

THE EFFECT OF β-CARYOPHYLLENE ON ISOPROTERENOL-INDUCED MYOCARDIAL INFARCTION

by

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Date & Venue

11:00 AM

Sunday, 31 May 2020

Black Board Session

https://eu.bbcollab.com/collab/ui/session/guest/34e6e19299c041ecb93657f5d602db84

Abstract

Cannabinoid type 2 receptors (CB2), a key member of the endocannabinoid system has recently emerged as a crucial therapeutic target for cardiovascular diseases (CVDs). Downregulation of CB2 receptors has been witnessed in various cancers, neurological and cardiovascular disorders. Thus, the activation of CB2 receptors may protect against ISO induced myocardial infarction (MI) in rats. The present study investigates the cardioprotective effect of a selective cannabinoid type 2 receptor agonist β-caryophyllene (BCP), a dietary phytocannabinoid and a natural bicyclic sesquiterpene against isoproterenol (ISO)-induced MI in rats. Male albino Wistar rats were pre- and co-treated with β-caryophyllene (50 mg/kg, orally) twice daily for 10 days along with the subcutaneous injection of ISO (85 mg/kg) at an interval of 24 h for two days (9th and 10th day). AM630 (1 mg/kg), a CB2 receptor antagonist was injected intraperitoneally as a pharmacological challenge prior to BCP treatment to demonstrate CB2 receptor-mediated cardioprotective mechanisms of BCP. ISO induced MI showed a significant decline in cardiac function, elevated levels of serum cardiac marker enzymes and enhanced oxidative stress markers with increased lipid peroxidation. Isoproterenol also induced pro-inflammatory cytokines release following activation of the nuclear factor kappa-B. Furthermore, a significant rise was also observed in the levels of inflammatory mediators, namely cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in ISO-challenged rats. Additionally, Isoproterenol also increased expression of proapoptotic (Bax, and active caspase-3) proteins along with the decreased expression of anti-apoptotic protein, Bcl2 and Bcl-xL in the myocardium. β-caryophyllene treatment resulted in significant protective effects on all biochemical and molecular parameters analyzed. Histopathological and ultrastructural evidence was found in line with our findings. Treatment with AM630, a potent CB2 receptor antagonist abrogates protective effects of BCP on all the biochemical and molecular parameters analyzed in ISO induced MI in rats. Thus, our study revealed that BCP protects the myocardium against ISO induced MI by attenuating oxidative stress, apoptosis and inflammation and the underlying mechanism of this protection is the activation of CB2 receptors. CB2 receptor selective compounds may provide a new potential class of cardioprotective drugs. The pharmacophore of these compounds could be used for synthesizing leads in drug discovery and development.

Keywords: Myocardial infarction, Phytochemical, Natural product, Cannabinoids, β-Caryophyllene, cannabinoid receptor type 2, Isoproterenol, Catecholamine.