British Journal of Pharmacology / Accepted Articles

RESEARCH PAPER

Cannabidiol protects against high glucose-induced oxidative stress and cytotoxicity in cardiac voltage-gated sodium channels

Mohamed A. Fouda, Mohammad-Reza Ghovanloo, Peter C. Ruben

First published:19 February 2020
https://doi.org/10.1111/bph.15020

Abstract

Background and purpose

Cardiovascular complications are the major cause of mortality in diabetic patients. However, the molecular mechanisms underlying diabetes-associated arrhythmias are unclear. We hypothesized that high glucose, could adversely affect Nav1.5, the major cardiac sodium channel isoform of the heart, at least partially via oxidative stress. We further hypothesized that cannabidiol (CBD), one of the main constituents of *Cannabis sativa*, through its effects on Nav1.5, could protect against high glucose elicited oxidative stress and cytotoxicity.

Experimental approach

To test these ideas, we used Chinese hamster ovarian (CHO) cells transiently co-transfected with cDNA encoding human Nav1.5 α-subunit under control and high glucose conditions (50 or 100 mM for 24 hours). Several experimental and computational techniques were used including: voltage-clamp of heterologous expression systems, cell viability assays, fluorescence assays, and action potential modelling.

Key Results

High glucose evoked cell death associated with elevation in reactive oxygen species, right shifted the voltage dependence of conductance and steady state fast inactivation and increased persistent current leading to computational prolongation of action potential (hyperexcitability) which could result in long QT3 arrhythmia. CBD mitigated all the deleterious effects provoked by high glucose. Perfusion with Lidocaine (a well-known sodium channels inhibitor with anti-oxidant effects), or co-incubation of Tempol (a well-known anti-oxidant) elicited protection, comparable to CBD, against the deleterious effects of high glucose.

Conclusions and implications

These findings suggest that, through its favourable anti-oxidant and sodium channel inhibitory effects, CBD may protect against high-glucose induced arrhythmia and cytotoxicity.

Supporting Information

Filename	Description

Filename	Description
0-sup-0001-Figure_S1.jpg	assay of the generation of ROS after 24 hours incubation. (A) Effect of gradual increasing of glucose concentration (10, 25, 50, 100, 150 mM) or mannitol (100 mM) on the cell viability of mock transfected or Nav1.5 stably transfected cells. (B) Effect of gradual increasing of glucose concentration (10, 25, 50, 100, 150 mM) or mannitol (100 mM) on ROS production of mock