The cannabinoid receptor type two is a therapeutic target for muscular dystrophy cardiomyopathy.

Authors:
A Gowran1, E Castiglioni1, D Rovina1, F Casalnuovo1, P Nigro1, P Spinelli2, R Visone2, M Rasponi2, A Redaelli2, G Pompilio3, 1Cardiology Center Monzino IRCCS, Unit of Vascular Biology and Regenerative Medicine - Milan - Italy, 2Milan Polytechnic , Department of Electronics, Information and Bioengineering - Milan - Italy, 3Cardiology Center Monzino IRCCS, Department of Cardiac Surgery - Milan - Italy,

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Muscular dystrophy (MD) is a genetic disorder affecting skeletal and cardiac muscle which arises due to abnormalities in the dystrophin (DMD) gene. These mutations alter the expression of the dystrophin protein causing metabolic and structural abnormalities in cardiomyocytes (CMs) which manifest clinically as cardiomyopathy and premature death from heart failure. There are two main forms of MD, Duchenne and Becker, which have disparate clinical onsets; childhood or middle adulthood respectively. The endogenous cannabinoid system is present throughout the human body. Considerable evidence indicate that its dysfunction is involved in several cardiovascular diseases e.g., cardiomyopathy induced by doxorubicin, diabetes or advanced liver cirrhosis. The endocannabinoid signalling network comprises: G-protein coupled receptors (types 1 and 2), endogenous ligands (anandamide and 2-arachidonoylglycerol) and regulatory proteins (fatty acid amide hydrolase and monoacylglycerol lipase). In the present study we show that Duchenne and Becker MD patients’ CMs derived from induced pluripotent stem cells (CMs-d-iPSCs) recapitulate MD cardiomyopathy as indicated by: out-of-frame/in-frame DMD mutations, altered dystrophin protein expression, increased intracellular Ca2+ and reactive oxygen species (ROS), sensitivity to substrate mechanics, and release of the cardiac damage protein cardiac troponin I (cTnI). Furthermore we also demonstrate that endocannabinoid levels and expression of the cannabinoid receptor type 1 are altered in Duchenne and Becker MD patients’ CMs-d-iPSCs. We then targeted the cannabinoid receptor type 2 as it is devoid of psychoactivity and has been shown to be cardioprotective in a number of in vitro and in vivo models of various cardiovascular diseases. Treatment with the potent and selective cannabinoid receptor type two agonist (JWH-133, 1µM) protected Duchenne and Becker MD patients’ CMs-d-iPSCs against increased levels of ROS and displayed reduced cTnI release (Figure 1). Collectively these results imply that targeting the cannabinoid receptor type two is a promising therapeutic avenue for MD cardiomyopathy.
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