Deleterious effects of FAAH-deficiency on development of ischemic cardiomyopathy in mice

Authors:
L Verfuether¹, P Zimmermann¹, A Zimmer², B Lutz³, L Bindila³, C Weisheit⁴, S Frede⁴, A Welz¹, O Dewald¹, GD Duerr¹, ¹University Hospital of Bonn, Department of Cardiac Surgery - Bonn - Germany, ²University of Bonn, Institute of Molecular Psychiatry - Bonn - Germany, ³University Medical Center of Mainz, Institute of Physiological Chemistry - Mainz - Germany, ⁴University Hospital Bonn, Department of Anesthesiology - Bonn - Germany,

Topic(s):
Basic Science - Cardiac Biology and Physiology: Metabolism

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S23

Introduction: Ischemic cardiomyopathy is associated with repetitive ischemia and reperfusion (I/R), which leads to inflammatory reaction and left ventricular (LV) dysfunction. Animal studies provided evidence for cardioprotective effects of the endocannabinoid system after myocardial ischemia including modulation of cardiomyocyte adaptation, inflammation and remodeling. Endocannabinoid receptor CB2-deficiency led to increased cardiomyocyte apoptosis and infarct size, accompanied by worsened LV function. Otherwise, endocannabinoids can act as Peroxisome proliferator-activated receptor (PPAR)-a agonist, and its activation causes lipotoxicity leading to cardiomyocyte apoptosis.

Purpose: Therefore, we investigated the impact of elevated level of endocannabinoid anandamide in fatty acid amide hydrolase (FAAH)-/- mice undergoing repetitive I/R.

Methods: Repetitive daily 15 min. left anterior descending artery occlusion was repeated over 1, 3 and 7 d in C57/Bl6 (WT) and FAAH-/- mice (n=8). PPAR-a mediated effects of high anandamide levels in FAAH-/- mice were eliminated with selective PPAR-a antagonist GW6471 i.v. Proof of principle was done by blocking the effect of agonist WY14,634 on PPAR-a downstream gene-upregulation with antagonist GW6471 in WT. LV function was assessed using M-mode echocardiography. Immunohistochemical analysis revealed collagen deposition (Picrosirius red), macrophage accumulation (MAC-2) and remodeling (aSMAC). Hypertrophy was determined by cardiomyocyte area and heart weight/tibia length. Molecular analyses involved Taqman® RT-qPCR and ELISA.

Results: FAAH-/- mice showed cardiomyocyte loss after 7 d I/R, accompanied by collagen deposition and scar formation with persistent LV dysfunction 60 d after discontinuation of I/R, while WT mice functionally and morphologically recovered after 60 d. Collagen deposition was reduced to WT-levels when FAAH-/- mice were treated with PPAR-a antagonist GW6471. Expression of chemokine CCL2 was significantly higher in FAAH-/- mice and accompanied by higher macrophage infiltration in areas of cardiomyocyte loss, which was also attenuated by GW6471 and comparable to WT. Significantly reduced induction of cardioprotective antioxidative enzyme HMOX-1 and energetically more efficient myosin heavy chain isoform ß-MHC in FAAH-/- mice was normalized to WT-level by GW6471. Further, hypertrophy and adverse remodeling with high myofibroblasts accumulation observed in FAAH-/- mice was diminished by PPAR-a antagonism.

Discussion: Our study gives novel insights in the role of endocannabinoids acting – at least in part – via PPAR-a in murine ischemic heart. We hypothesize that uncontrolled increase in endocannabinoids may have detrimental effects on cardiomyocyte survival due to PPAR-a activation with lipotoxicity and subsequent increase in inflammatory response.
Abstract: Deleterious effects of FAAH-deficiency on development of ischemic cardiomyopathy in mice

Authors: L Verfuhr1, P Zimmermann1, A Zimmer2, B Lutz3, L Bindila3, C Weisheit4, S Frede4, A Welz1, O Dewald1, GD Duerr1

1 University Hospital of Bonn, Department of Cardiac Surgery - Bonn - Germany,
2 University of Bonn, Institute of Molecular Psychiatry - Bonn - Germany,
3 University Medical Center of Mainz, Institute of Physiological Chemistry - Mainz - Germany,
4 University Hospital Bonn, Department of Anesthesiology - Bonn - Germany,

Introduction: Ischemic cardiomyopathy is associated with repetitive ischemia and reperfusion (I/R), which leads to inflammatory reaction and left ventricular (LV) dysfunction. Animal studies provided evidence for cardioprotective effects of the endocannabinoid system after myocardial ischemia including modulation of cardiomyocyte adaptation, inflammation and remodeling. Endocannabinoid receptor CB2-deficiency led to increased cardiomyocyte apoptosis and infarct size, accompanied by worsened LV function. Otherwise, endocannabinoids can act as Peroxisome proliferator-activated receptor (PPAR)-α agonist, and its activation causes lipotoxicity leading to cardiomyocyte apoptosis.

Purpose: Therefore, we investigated the impact of elevated level of endocannabinoid anandamide in fatty acid amide hydrolase (FAAH)-/ mice undergoing repetitive I/R.

Methods: Repetitive daily 15 min. left anterior descending artery occlusion was repeated over 1, 3 and 7 d in C57/Bl6 (WT) and FAAH-/- mice (n=8). PPAR-α mediated effects of high anandamide levels in FAAH-/- mice were eliminated with selective PPAR-α antagonist GW6471 i.v. Proof of principle was done by blocking the effect of agonist WY14,634 on PPAR-α downstream gene-upregulation with antagonist GW6471 in WT. LV function was assessed using M-mode echocardiography. Immunohistochemical analysis revealed collagen deposition (Picrosirius red), macrophage accumulation (MAC-2) and remodeling (aSMAC). Hypertrophy was determined by cardiomyocyte area and heart weight/tibia length. Molecular analyses involved Taqman® RT-qPCR and ELISA.

Results: FAAH-/- mice showed cardiomyocyte loss after 7 d I/R, accompanied by collagen deposition and scar formation with persistent LV dysfunction 60 d after discontinuation of I/R, while WT mice functionally and morphologically recovered after 60 d. Collagen deposition was reduced to WT-levels when FAAH-/- mice were treated with PPAR-α antagonist GW6471. Expression of chemokine CCL2 was significantly higher in FAAH-/- mice and accompanied by higher macrophage infiltration in areas of cardiomyocyte loss, which was also attenuated by GW6471 and comparable to WT. Significantly reduced induction of cardioprotective antioxidative enzyme HMOX-1 and energetically more efficient myosin heavy chain isoform β-MHC in FAAH-/- mice was normalized to WT-level by GW6471. Further, hypertrophy and adverse remodeling with high myofibroblasts accumulation observed in FAAH-/- mice was diminished by PPAR-α antagonism.

Discussion: Our study gives novel insights in the role of endocannabinoids acting – at least in part – via PPAR-α in murine ischemic heart. We hypothesize that uncontrolled increase in endocannabinoids may have detrimental effects on cardiomyocyte survival due to PPAR-α activation with lipotoxicity and subsequent increase in inflammatory response.