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CB2 receptor influences adaptation of cardiomyocytes to hypoxia and their survival during inflammatory stress in vitro
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Purpose: The endocannabinoid system and cannabinoid receptor CB2 have been associated with modulation of inflammatory response and myocardial adaptation after ischemic injury. We recently demonstrated activation of endocannabinoid system and CB2 receptor being associated with inflammatory response in patients with myocardial hypertrophy due to aortic stenosis. Therefore we evaluated CB2 effects on cardiomyocytes and macrophages in cell culture under stress conditions in vitro.

Methods: Murine embryonic (eCM) and adult (CM) cardiomyocytes as well as murine macrophages (MO) were derived from wildtype- (WT) and CB2-deficient (CNR2(-/-)) mice and cultured under normoxia and hypoxic conditions (2% O2). We investigated each cell line in separate cultures as well as in co-culture of MOs and eCMs in order to analyse the impact of inflammation on eCM survival. Immunohistochemical and molecular analysis (qPCR) were performed. MO proliferation was assessed using CFSE, migration in Boyden chamber and phagocytosis activity with FITC-dextrane uptake.

Results: We found a significant induction of CB2 receptor mRNA and protein in both murine cardiomyocytes (eCMs & CMs) and MOs in vitro following the cultivation under hypoxic conditions and/or stimulation with pro-inflammatory interferon g. CNR2(-/-)-CMs showed a significantly higher level of conglutinated, non-vital CMs after incubation under hypoxic conditions when compared to respective WT-CMs. CNR2(-/-)-eCMs showed a significantly less induction of cardioprotective superoxide dismutase 3 under hypoxic conditions. We observed a prolonged proliferation, a significantly stronger migration, but less phagocytosis potential in CNR2(-/-)-MOs than in corresponding WT-cultures. Co-culture revealed a significantly higher loss of eCMs and an induction of their apoptosis after cultivation with CNR2(-/-)-MOs due to their TNF-a and caspase-3 induction.

Conclusions: CB2 receptor seems to provide cardioprotection under hypoxia through a complex mechanism including induction of superoxide dismutase 3 in cardiomyocytes and modulation of macrophage function via release of pro-apoptotic factors, thus contributing to survival of cardiomyocytes.