β3AR-dependent BDNF generation limits chronic post-ischemic heart failure

Seungho Jun, Alessandro Cannavo,¹ Giuseppe Rengo,¹ Federica Marzano,² Jacopo Agrimi,³ Gizem Keceli,⁴ Andrea Elia,¹ Daniela Liccardo,¹ Giovanna G. Altobelli,¹ Erhe Gao,⁵ Ning Feng,⁶ Walter Koch,⁷ and Nazareno Paolocci⁸

¹University of Naples Federico II; ²Federico II Univ, Naples; ³University of Padova; ⁴Johns Hopkins University Medical Institutions; ⁵Temple University; ⁶University of Pittsburgh; ⁷Temple Univ School of Medicine; and ⁸Johns Hopkins Medical Institutions

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Rationale: Lack of brain-derived neurotrophic factor (BDNF) and/or inadequate expression/activity of its associated tropomyosin kinase receptor B (TrkB) account for brain and cardiac disorder. While β-adrenergic receptor (β3AR) is responsible for the local expression of BDNF in neurons, whether a similar interaction is observed and pathophysiologically relevant in the cardiovascular system is unknown, especially in the post-ischemic myocardium with adrenergic desensitization. Moreover, it is unclear whether and how TrkB agonists counter chronic post-ischemic left ventricle (LV) decompensation.

Methods: We conducted in vitro studies with neonatal rat (NRVM)/adult murine cardiomyocytes (CMs), SH-SY5Y neuronal cells, and umbilical vein endothelial cells. We assessed the degree of impact from ischemia-related injury via either in vivo coronary ligation (myocardial infarction, MI) or ex vivo isolated hearts with global ischemia-reperfusion injury (I/R) in WT, cardiomyocyte-selective BDNF KO (myoBDNF KO) or β3AR KO mice.

Results: In WT hearts, early after MI (in vitro, the TrkB agonist, LM22A-4 promoted neurite outgrowth and neovascularization. Moreover, LM22A-4 and another agonist, TrkB, 7,8-dihydroflavone enhanced myocyte contractility. When given to in vivo MI mice, LM22A-4 rescued, at least in part, LV dysfunction, denervation, and hypovascularity. Of note, when given to isolated myoBDNF KO hearts, it no longer benefited post-I/R LV structure and function. Superfusing isolated murine myocyte with the β3AR-agonist, BRL-37344 enriched these cells with BDNF. Moreover, BRL-37344 limited post-I/R injury in WT mice but not in myoBDNF KO ones. Finally, the β1AR blocker that upregulates β3AR, augmented BDNF levels in the ischemic myocardium, improving in vivo post-MI dysfunction.

Conclusions: Lack of BDNF accounts, at least in part, for chronic post-ischemic LV decompensation. By extension, by restoring intracardiac BDNF levels, TrkB agonists can limit the extent of ischemic injury, both in vivo and ex-in vivo. Direct and indirect cardiac β3AR stimulation via BRL-37344 or β-blocker, metoprolol, respectively, show another BDNF-centered means to arrest chronic post-ischemic HF. These findings may have relevant pharmacological implications for the treatment of chronic post-ischemic LV decompensation.