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PTH treatment after myocardial infarction in mice attenuates late ischemic cardiomyopathy: impact of bone marrow derived versus cardiac stem cells

Huber B¹, Zaruba MM¹, Brunner S¹, Deindl E², David R¹, Fischer R¹, Assmann G³, Mueller-Hoecker J³, Franz WM¹

¹Medical Department I, Klinikum Grosshadern, Ludwig Maximilians University (LMU), Munich, Germany
²Institute of Surgical Research, LMU, Munich, Germany
³Institute of Pathology, LMU, Munich, Germany

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Introduction:

Bone marrow (BM) derived stem cells improve cardiac function after myocardial infarction (MI). Recently, parathyroid hormone (PTH) was shown to regulate the stem cell niche in the bone marrow. Therefore, in a murine model of MI we analyzed the influence of PTH treatment on survival, functional parameters as well as stem cell homing to the heart.

Material and Methods:

12-24 h after MI, PTH was injected daily for two weeks. 6 and 30 days after the surgical procedure, pressure volume relationships were investigated in vivo. Heart tissues were investigated by immunohistochemistry and RT-PCR. Cardiac Homing was studied by flow cytometry.

Results:

PTH treatment resulted in a significant improvement of post MI survival and myocardial function associated with less reduction of LV wall thickness and smaller infarct size. These effects were mediated by an enhanced homing of CXCR4 enriched CD45+/CD34+ BM derived stem cells into the ischemic heart facilitated by a PTH mediated upregulation of SDF-1a. However, infiltrated inflammatory CD45+/CD34- cells revealed a strongly reduced expression of CXCR4. In contrast to the BM niche, myocardial ischemia alone or after PTH treatment did not promote proliferation of resident cardiac CD45-/CD34-/c-kit+ and even decreased the number of CD45-/CD34-/Sca-1+ stem cells in the heart. Immunohistologically, PTH treated hearts revealed an increased neovascularization of CD31+ capillaries in the borderzone, which could be explained by an upregulation of VEGF-A and VEGF-receptor1 mRNA. Furthermore, PTH treatment enhanced expression of IGF-1 receptor protein primarily localized on cardiomyocytes in the borderzone, which was related to a reduced number of apoptotic cells.
Conclusion:

PTH treatment after MI exerts beneficial effects on survival and myocardial function associated with an augmented homing of CXCR4 enriched CD45+/CD34+ stem cells towards an increased SDF-1α gradient in the myocardium. Paracrine effects of these cell populations correlated with an improved neovascularization and cell survival via VEGF and IGF-1 dependent pathways. Since PTH is already used in patients with osteoporosis our findings may have direct impact on the initiation of clinical studies in patients with ischemic heart disease.