UKE Paper of the Month Oktober 2018

Precursor proadrenomedullin influences cardiomyocyte survival and local inflammation related to myocardial infarction

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PNAS

ABSTRACT: Increased adrenomedullin (ADM) levels are associated with various cardiac diseases such as myocardial infarction (MI). ADM is cleaved off from the full-length precursor protein pro-adrenomedullin (ProADM) during its post-translational processing. To date, no biological effect of ProADM is reported, while ADM infusion leads to anti-apoptotic effects and improved cardiac function. Using an MI mouse model, we found an induction of ProADM gene as well as protein expression during the early phase of MI. This was accompanied by apoptosis and increasing inflammation, which substantially influence the post-MI remodeling processes. Simulating ischemia in vitro, we demonstrate that ProADM expression was increased in cardiomyocytes and cardiac fibroblasts. Subsequently, we treated ischemic cardiomyocytes with either ProADM or ADM and found that both proteins increased survival. This effect was diminishable by blocking the ADM_1 receptor. To investigate whether ProADM and ADM play a role in the regulation of cardiac inflammation, we analyzed chemokine expression after treatment of cells with both proteins. While ProADM induced an expression of pro-inflammatory cytokines, thus promoting inflammation, ADM reduced chemokine expression. On leukocytes, both proteins repressed chemokine expression revealing anti-inflammatory effects. However, ProADM but not ADM dampened concurrent activation of leukocytes. Our data show that the full-length precursor ProADM is biologically active by reducing apoptosis to a similar extent as ADM. We further assume that ProADM induces local inflammation in affected cardiac tissue but attenuates exaggerated inflammation, whereas ADM has low impact. Our data suggest that both proteins are beneficial during MI by influencing apoptosis and inflammation.

STATEMENT: *Our work was selected for publication in PNAS which is a general science journal and all papers are intelligible to a broad and interdisciplinary scientific audience. Svenja Hinrichs et al. found that pro-adrenomedullin (ProADM), the putatively inactive protein precursor of the hormone adrenomedullin (ADM), has a biological active function by increasing cell survival during ischemia. ProADM exhibited pro-inflammatory effects in cardiac fibroblasts, unlike ADM, but anti-inflammatory effects in activated immune cells. The results suggest that ProADM is biologically active and prevents cell death during myocardial infarction by regulating inflammation in conjunction with ADM. In particular, our submitted cover image was selected to grace the respective issue No. 115-37.*

BACKGROUND: This work was performed at the clinic for general and interventional cardiology in the group of Diana Lindner & Dirk Westermann, who holds a professorship at UKE since 2017. It was part of the PhD thesis of Dr. hum. biol. Svenja Hinrichs within the DZHK research project “Molecular mechanisms of heart failure”. The scientists Diana Lindner and Dirk Westermann have a specific focus on the underlying molecular mechanisms in the development of heart failure and specific target genes or proteins that improve cardiac function by influencing cardiac inflammation and fibrosis.