Abstract: **P283**

The precursor Pro-Adrenomedullin is an active protein: it supports cardiomyocyte survival and regulates cardiac inflammation related to myocardial infarction

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Background:
Adrenomedullin (ADM) is increased in plasma from patients with myocardial infarction (MI). Initially, it is produced by cardiac cells as an assumed inactive precursor protein Pro-Adrenomedullin (ProADM), and post-translationally processed to mature and biologically active ADM. In first data, patients with MI showed beneficial effects from ADM treatment. The aim of our study was to examine the biological effect behind upregulated ProADM during MI on cardiac cells. Furthermore, we examined ProADM and ADM as potential therapeutic targets regarding cardiomyocyte apoptosis and inflammation, which occurs during the acute phase after MI.

Results:
Protein and mRNA levels of ProADM were highly upregulated after MI in the cardiac tissue of mice. To examine the cell source, we measured gene expression of proAdm by qPCR after simulated ischemia in cardiac cells, and detected elevated expression levels in cardiomyocytes (11.3±0.9 fold p<0.0001) and cardiac fibroblasts (5±1.2 fold p<0.0001). Activated inflammatory cells (splenocytes) increased the expression as well (2.9±0.2 fold p<0.0001). We showed, that ProADM is secreted as a non-processed protein. Therefore, we treated ischemic cardiomyocytes with recombinant ProADM or ADM. Both proteins supported cardiomyocyte survival by increasing vitality of cells and decreasing caspase 3/7 activity significantly. This function is mediated by the same cell surface receptors. Regarding cardiac inflammation, we stimulated cardiac fibroblasts and inflammatory cells with both proteins. ADM decreased Ccl2 expression in inflammatory cells (-1.3 ± 0.1 fold p<0.05) and cardiac fibroblasts (-1.5 ± 0.1 fold p<0.01). ProADM also led to decreased expression in inflammatory cells (-1.4 ± 0.08 fold p<0.01). In contrast to this, stimulation of cardiac fibroblasts with ProADM led to increased Ccl2 expression (7.3 ± 0.5 fold p<0001). To simulate inflammatory induction after MI, we used secreteme from ischemic cardiac fibroblasts to activate inflammatory cells, and observed elevated gene expression of Ccl2 (6.9 ± 2.8 fold p<0.05). ProADM but not ADM treatment suppressed the secreteme induced upregulation of Ccl2 (1.5 ± 0.4 fold p<0.01).

Conclusion:
ProADM was highly upregulated after MI in the cardiac tissue and in ischemic cardiac cells. Our experiments revealed that the assumed inactive ProADM is indeed a functional protein. ProADM as well as its cleaved mature form ADM supported cardiomyocyte survival during simulated ischemia, which indicated their potential to mimic ADM beneficial effects in cardiovascular diseases.
as a therapeutic drug for MI patients. Furthermore, ProADM showed cell-specific and opposite effect to ADM regarding inflammation. ADM had anti-inflammatory effects on cardiac cells. Whereas, ProADM induced chemokine expression in cardiac fibroblasts and could therefore led to recruitment of inflammatory cells. On the other hand, ProADM but not ADM reduced chemokine expression in activated inflammatory cells and could therefore damp established cardiac inflammation.