

MTP-131, a cardiolipin-targeting peptide, improves mitochondrial activity in the failing human heart

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Background: Mitochondrial dysfunction contributes to myocellular abnormalities in the failing human heart. We have previously shown significant abnormalities in cardiolipin content and electron transport chain complexes in failing human heart. MTP-131 (elamipretide) is a mitochondria-targeting peptide currently being investigated in several Phase 2 clinical trials for heart failure. In animal models of heart disease, MTP-131 improved cardiac and mitochondrial function through a mechanism involving stabilization of cardiolipin-dependent respiration.

Purpose: To determine whether MTP-131 treatment of the human failing heart improves mitochondrial function, assessed at different sites along the respiratory chain. **Methods:** Ventricular tissue was rapidly harvested at the time of cardiac transplantation for end-stage heart failure secondary to idiopathic dilated cardiomyopathy (F), or from age-matched donor hearts (NF) not implanted for technical reasons. Tissue was either immediately used for respirometry or rapidly frozen at -80C. In fresh tissue, mitochondrial Complex I- and II-dependent respiration was determined using high-resolution respirometry. Total Complex IV activity was determined using spectrophotometric assays. From frozen samples, Complex IV in-gel activity assays were performed in Blue Native (BN)-PAGE to determine activity attributed to within the supercomplex (SCIV) or from uncomplexed, free Complex IV (FCIV). **Results:** State 3 respiration (in pmol/(s*mg)) was lower in F than NF when mitochondria were respiring via Complex I- or II-dependent substrates (glutamate/malate: 40 ± 11 vs 75 ± 6 ; succinate: 64 ± 16 vs 108 ± 11). MTP-131 treatment improved state 3 respiration in F mitochondria at both complexes I and II (glutamate/malate: 74 ± 6 ; succinate: 125 ± 13), but did not alter respiration in NF mitochondria under any substrate conditions. In BN-PAGE studies, SCIV activity was 30% lower ($P < 0.05$) in F compared to NF-samples, but unchanged in the FCIV fraction. MTP-131 treatment increased SCIV activity ($P < 0.05$) but did not change FCIV activity, suggesting that MTP-131-mediated improvements in respiration occur in mitochondrial supercomplexes. MTP-131 treatment of freshly-isolated F mitochondria increased Complex IV activity by 50% ($P < 0.01$). **Conclusion:** MTP-131 treatment improves mitochondrial function at the level of the individual complex, supercomplex and intact mitochondria in the failing human heart. These findings suggest that stabilizing cardiolipin-dependent respiratory complexes represents a novel treatment for improving mitochondrial function in heart failure.