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Glucose-insulin and sphingosine-1-phosphate therapy against de novo AHF: two new approaches to treatment of acute heart failure (AHF)
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Purpose: Acute heart failure (AHF) is a clinical emergency, with high mortality and re-hospitalizations. We established a model of de novo AHF to study the molecular survivor activating factor enhancement (SAFE) pathway activated by sphingosine-1-phosphate (S1P), a component of HDL. S1P activates SAFE pathway by binding to its receptors which via the phosphorylation of signal transducer and activator of transcription 3 (STAT3) translocate to the nucleus and promote cell survival and improve recovery. We tested the involvement of the S1P-activated SAFE pathway in rat hearts subjected to de novo AHF. We also examined the combined effect of metabolic therapy by glucose-insulin (GI) and S1P.

Methods: AHF was induced by reducing aortic perfusion pressure of the Langendorff perfused rat heart from 100 cm H2O to 20 cm H2O. Acute stress was imposed in the AHF phase by low glucose (2.5mmol/L) and elevating free fatty acids (FFA) (1.3mmol/L), thus creating combined hypotensive and metabolic stress. GI 11.1mmol/L and 0.3mU respectively was added in the recovery phase following AHF. Treatment by AG490, a pharmacological inhibitor of SAFE, and by Western blots for activation of signal transducer and activator of transcription 3 (STAT3).

Results: S1P improved the heart rate (HR) versus controls (148.8 ± 26.4 vs. 37.9 ± 9.7; n=6; p<0.01) BPM. Treatment by AG490 reduced heart rate vs. S1P (42.3 ± 17.1 vs. 148.8 ± 26.4; p<0.05 vs. S1P+AG490; n=6). STAT3 was increased (p<0.05) in the nuclear fraction in hearts treated with S1P vs. those treated with S1P+AG490. There was no change in the LV developed pressure. Combined GI and S1P in the recovery phase improved HR vs. controls (214.4 ± 19.2 vs. 66.5 ± 22.6 BPM; p<0.001 vs. controls; n=8) and improved LV developed pressure, indicating better contractility (177.2 ± 38.6 vs. 20.5 ± 8.3 mmHg; p<0.001 vs. controls; n=8).

Conclusions: S1P activates the SAFE pathway by upregulating STAT3 in the nuclear fraction in model de novo AHF and improves cardiac function by increasing HR, thus indicating enhanced sinus node activity. The combination of metabolic GI and molecular S1P therapies improves HR and contractility, thus suggesting principles of future therapy against AHF.