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CO-ACTIVATION OF NUCLEAR FACTOR-KB AND MYOCARDIN/SERUM RESPONSE FACTOR IN CANINE CARDIAC MYOBLASTS EXPOSED TO HIGH LEVELS OF INSULIN

ACC Poster Contributions
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Background: Hyperinsulinemia in metabolic syndrome and diabetes contributes to the development of cardiac hypertrophy and heart failure. In patients with insulin resistance high circulating levels of tumor necrosis factor (TNF)-α may synergize with insulin in proinflammatory signaling for cardiac hypertrophy, apoptosis, and fibrosis. High levels of TNF and insulin also impacts on expression of myogenic transcription factors, such as myocardin A (MYCD) and serum response factor (SRF). This study aimed at testing whether high insulin levels affect activation of TNF-induced NF-κB and MYCD/SRF for hypertrophy-signaling in canine cardiac myoblasts (CM).

Methods and **Results:** Treatment of CM with high insulin (10-8-10-7 M) for 0-24 h determined increased insulin receptor substrate (IRS)-1 phosphorylation at Ser307. Under these conditions, high insulin (10-8 M or higher) markedly decreased protein levels of CHIP (- Δ%: 68 ± 13 of control, $p<0.05$ n=3) and increased the activity of SRF and expression of β-MHC and early promyogenic transcription factors Nkx 2.5, GATA-4, DTEF, MLC2V and MYCD (Δ%:82 ± 30, 65 ± 10, 74 ± 10, 60 ± 22, 59 ± 15, 60 ± 10 of control respectevely, $p<0.05$ n=3, as determined by qRT-PCR), effects partially reverted by Akt inhibitor LY379196. siRNAs to MYCD prevented, while siRNA-mediated CHIP disruption potentiated high insulin-induced serum response element (SRE) activation. Insulin markedly increased TNF-α-induced NF-κB activation and nuclear expression of p65 subunit, effects reverted by the proteasome inhibitor MG132. In the hearts of db/db diabetic mice, Akt phosphorylation was decreased, whereas p38MAPK and IRS-1 phosphorylation at Ser307 were strongly increased, indicating a selective MAPK-dependent insulin resistance. Under these conditions, the expression of MYCD and activities of SRE and NF-kB were increased.

Conclusion: Responding to stimulation of high levels of insulin, myoblasts have increased expression of MYCD/SRF in a CHIP dependent manner. The high insulin treatment also enhances TNF activation of NF-κB. MYCD acts as a nuclear effector of the insulin signaling leading to a transcriptional program for cardiac hypertrophy during hyperinsulinemia.