TETRAHYDROBIOPTERIN RESTORES CARDIOPROTECTION BY ISCHEMIC PRECONDITIONING DURING HYPERGLYCEMIA THROUGH PROTEIN S-NITROSYLATION

ACC Poster Contributions
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Background: The mechanism of loss of cardioprotection by IPC during hyperglycemia (HG) remains unclear. Because protein S-nitrosylation by nitric oxide (NO) has been implicated in cardioprotection afforded by IPC, we hypothesized that the deficiency of tetrahydrobiopterin (BH4), a co-factor of NO synthase (NOS), and the resultant decrease in bioavailable NO and protein S-nitrosylation is responsible for the loss of cardioprotective effects mediated by IPC during HG.

Methods: Isolated rat hearts were perfused in normal glucose (NG; 5.5 mM) or high glucose (HG; 20 mM) conditions and underwent IPC with 3 cycles of 5 min ischemia and 5 min reperfusion before 30 min ischemia followed by 2 hrs reperfusion. A superoxide scavenger tempol (100 μM) or a thiol-reducing agent dithiothreitol (DTT; 1 mM) was administered during IPC.

Results: IPC improved post-ischemic LV function and reduced infarct size in the heart with NG but not in the heart with HG. Hyperosmotic perfusion with mannitol (20 mM) did not affect cardioprotection by IPC. The cardioprotective effect of IPC in the heart with NG was associated with an increased NO bioavailability as demonstrated by an increase in cardiac tissue nitrate plus nitrite (NOx) and protein S-nitrosylation. BH4 was decreased in the heart with HG associated with enhanced superoxide generation and decreased NOx generation and protein S-nitrosylation. Although exogenous BH4 (10 μM) did not further increase NOx and protein S-nitrosylation nor did it enhance IPC-mediated cardioprotection in the heart with NG, it increased NOx and protein S-nitrosylation and inhibited superoxide generation associated with cardioprotection in the heart with HG. A NO-dependent guanylyl cyclase inhibitor ODQ (10 μM) had no effect on IPC-mediated cardioprotection. Tempol inhibited superoxide generation without an effect on protein S-nitrosylation and did not confer cardioprotection, while DTT blocked protein S-nitrosylation and IPC-mediated cardioprotection in the heart with HG and NG.

Conclusion: BH4 restores cardioprotection by IPC in the heart with HG by increasing bioavailable NO and protein S-nitrosylation.