NOVEL ACTIONS OF β2-ADRENORECEPTOR (β2-AR) STIMULATION IN MYOCARDIAL ISCHEMIA-REPERFUSION (MI/R) INJURY: ROLE OF NOS-DEPENDENT CARDIOPROTECTION

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Background: Recent studies have shown that β2-AR receptor activation protects cardiac myocytes from cell death. We hypothesized that acute β2-AR agonist therapy with arformoterol (ARF) would attenuate the severity of MI/R injury via NOS activation, and increased nitric oxide (NO) bioavailability.

Methods: Male C57/BL6J, iNOS KO and eNOS KO Mice (n=10-13 per group) underwent 45 min. of MI induced by transient LCA occlusion followed by 24 hrs. of R. ARF (1 μg/kg) or vehicle (VEH) was administered via intra cardiac injection at 5 min before R. Myocardial area-at-risk (AAR) per left ventricle (LV) and infarct size per area-at-risk (INF/AAR) were evaluated using Evan’s Blue and TTC at 24 hr. Cardiac troponin-I levels were also measured in serum following MI/R. Furthermore, cardiac tissue and plasma samples were collected from mice treated with ARF or VEH to evaluate NOS protein levels and phosphorylation status, AKT-P status, as well as circulating nitrite and nitrate levels.

Results: A dose of 1 μg/kg of ARF significantly reduced INF/AAR by 53.1% (p < 0.001 vs. VEH) and serum troponin-I levels were reduced from 37.1 ng/mL to 9.87 ng/mL (p < 0.01 vs. VEH). Furthermore, ARF treatment significantly increased AKT phosphorylation at Ser473 (p < 0.01 vs. VEH), eNOS-P at Ser1177 (p < 0.05 vs. VEH). Furthermore, total iNOS expression was also significantly (p < 0.02) increased as compared to VEH. ARF treatment significantly increased myocardial nitrite levels (p < 0.01 vs. VEH) at 2 hrs following injection. Interestingly, ARF failed to reduce INF size reduction in eNOS-/- mice and administration of a β2-AR blocker (ICI 118,551) or a NOS inhibitor (L-NAME) significantly abrogated ARF-mediated cardioprotection in MI/R.

Conclusions: Our results indicate that the β2-AR stimulation by ARF activates both AKT and eNOS, increases iNOS, and augments plasma and cardiac NO bioavailability. Thus, activation of β2-AR during MI/R may prove beneficial for the treatment of acute myocardial infarction.