**AMPLIFICATION OF THE MYOCARDIAL INFARCT SIZE LIMITING EFFECTS OF GLP-1 RECEPTOR ACTIVATION BY CILOSTAZOL, A PHOSPHODIESTERASE III INHIBITOR**

Y. Ye3, **Y. Birnbaum1,2,3**

1Dept. of Medicine, Baylor College of Medicine, 2Texas Heart Institute, St Luke's Episcopal Hospital, 3Dept. of Biochemistry and Molecular Biology, The University of Texas Medical Branch, Houston, TX, USA

Background: Glucagon-like Peptide (GLP1) analogues reduce myocardial infarct size (IS) in nondiabetic animals. Preconditioning of diabetic animals is limited. GLP1-receptor activation increases intracellular cAMP with downstream activation of protein kinase A (PKA). Cilostazol (CIL) prevents the degradation of cAMP and reduces IS. We assessed whether CIL augments the IS-limiting effects of exenatide (EX, a GLP1 analogue) and MK0626 (MK, a DPPP-4 inhibitor), by increasing intracellular cAMP in mice with type-2 diabetes.

Methods: Db/Db mice received oral CIL or vehicle by oral gavage. Experiment 1: mice received S.C. EX or vehicle 1h before surgery. Additional mice received H89, a PKA inhibitor, alone or with CIL+EX. Experiment 2: mice received 3-day pretreatment with MK (0, 1, 2 or 3mg/kg/d). Mice were subjected to 30min ischemia and 24h reperfusion. Results: EX, MK and CIL alone reduced IS. IS was significantly smaller when CIL was combined with either EX or MK. EX, MK and CIL alone increased myocardial cAMP levels and PKA activity. Both were further increased when CIL was combined with either EX or MK. H89, a PKA inhibitor completely blocked the IS-limiting effects of EX+ CIL. PKA activation led to decreased expression of PTEN with subsequent increased Akt and ERK 1/2 activation and eNOS phosphorylation.

Conclusion: GLP-1 receptor activation and CIL have additive IS-limiting effects in diabetic mice. The additive effects are related to cAMP induced PKA activation with downstream activation of Akt, Erk 1/2 and eNOS.