Lakshmi Pulakat, J Clin Exp Cardiolog 2016, 7:10(Suppl)
http://dx.doi.org/10.4172/2155-9880.C1.053

Cardiovascular protective effects of AT2R activation by a new peptide drug NP-6A4

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Statement of the Problem: Extensive clinical observations over the past decade have inextricably linked diabetes (DM) to cardiovascular disease (CVD) to an extent that an estimated 70% of all diabetics die from CVD complications. Despite significant clinical advances in CVD treatment, morbidity and mortality due to DM-associated CVD remains an important clinical challenge. Evidence suggests that AT2R, encoded by Agtr2 gene, improves cardiac repair after myocardial infarction. AT2R is an angiotensin II receptor and a member of the anti-inflammatory branch of renin-angiotensin system (RAS). Clinically, loss of AT2R expression in men due to the intronic G1675A or A1818T polymorphism is associated with increased arterial stiffness, and impaired kidney function. We hypothesized that an AT2R agonist that can elevate cardiovascular AT2R expression and activation in conditions of DM will protect patients from DM-associated CVD progression. There are no such drugs currently in standard of care. We reported recently that NP-6A4, an AT2R agonist developed by Novopyxis Inc., could increase the survival and viability of nutrient-stressed mouse and human cardiovascular cells better than beta-blockers and AT1 receptor blocker losartan. This study was performed to determine whether the protective effects of NP-6A4 are translational to a cardiac-impaired animal model (male Zucker Obese, ZO-M rat) a translational model for human CVD and type 2 diabetes (T2DM). We treated 11-week-old ZO-M rats exhibiting CVD with NP-6A4 (1.8mg/kg/day by subcutaneous delivery) for 2 weeks. This treatment improved several cardiac parameters including circumferential strain of endocardium ($p \leq 0.05$), myocardial performance index (MPI) ($p \leq 0.005$), and E/E' ratio ($p \leq 0.002$). NP-6A4 also reduced cardiomyocyte hypertrophy and fibrosis in ZO-M rats, and increased capillary density and AT2R expression in the heart ($p \leq 0.05$). Therefore, we conclude that NP-6A4 is an effective drug that can increase cardiovascular protective AT2R expression and mitigate DM-associated CVD.

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