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Glucose-dependent insulinotropic peptide is essential for maintenance of cardiac lipid metabolism via FGF21-dependent pathway

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Background/Introduction: Incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are secreted from the small intestine and emerged as important participants in glucose homeostasis that involves in the pathogenesis of type 2 diabetes (T2D). stimulate glucose-dependent insulin biosynthesis. Emerging data suggest important extrapancreatic functions for GLP-1 on cardiovascular system. However, limited evidence has been emerged whether GIP may play any pathophysiological role in heart. GIP promotes insulin secretion leading to augment insulin-induced lipogenesis. Recent research has highlighted the relevance of the GIP/GIPR axis in principal insulin-sensitive organs such as adipose tissue. Heart is another insulin-sensitive organ in which insulin promotes hypertrophy of myocardium presumably via activation of Akt pathway. In T2DM, ectopic accumulation of lipid and fat to myocardium that is known as “cardiac steatosis”; however, it remains uncertain whether the GIP/insulin axis may modulate cardiac steatosis observed in T2DM.
Purpose: To elucidate that physiological GIP may play a regulatory role in cardiac pathophysiology.
Methods: We employed mouse model of GIPR deficiency (GIPR-KO) that was generated by lacking the GIPR gene (GIPR), by replacing exons 4 and 5 of GIPR with the PGK-neo cassette. Cardiac evaluation of GIPR-KO was performed at the age of 6 week-old (w/o), 10 w/o, 23 w/o, and 53 w/o.
Results: GIPR deficient mice (GIPR-KO) exhibited normoglycemia, but their circulating free acid level and ketone level were elevated. Interestingly, GIPR-KO at younger age (6-week-old and 10-week old) exhibited normal left-ventricular (LV) function, however, older mice aged older than 20-week-old exhibited significant systolic left-ventricular dysfunction (FS (%) 55.2±1.9 for Wild-type, 32.1±2.6 for 23-w/o-GIPR-KO, 28.5±2.6 for 56-w/o-GIPR-KO, $P<0.01$). Histological analysis revealed that cardiomyocyte size was decreased and capillary density was increased in GIPR-KO. Interestingly, TUNEL staining revealed that there was no increase in cardiac apoptosis in GIPR-KO. In contrast, GIPR-KO exhibited increase in cardiac fibrosis (Picro-sirius staining) and oxidative stress (DHE staining). Myocardial triglyceride accumulation was decreased in GIPR-KO heart. QPCR analysis revealed GIPR-KO heart exhibited increase in BNP level and decline in fibroblast growth factor 21 (FGF-21), an hormonal activator for energy expenditure in adipocyte. GIP augmented FGF-21 expression in cardiomyocytes via PPARalfa.
Conclusion: Loss of GIP signaling caused impaired fatty acid metabolism in heart via impairment of FGF21 pathway and oxidative stress, leading to an age-dependent progression of cardiac dysfunction.