The aging-induced hyperexcretion of glucose-dependent insulinotropic peptide is essential for the healthy cardiac remodeling by prevention of cardiac ceramide accumulation

Y. Kureishi Bando, Y.R. Remina, T.K. Kamihara, K.N. Nishimura, T.M. Murohara

Nagoya University Graduate School of Medicine, Department of Cardiology, Nagoya, Japan
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Background: Glucose-dependent insulinotropic peptide (GIP) is incretin hormone that is emerged as an important regulator of lipid metabolism. Fat intake induces hypersecretion of GIP that is involved in obesity and ectopic fat accumulation. Aging is another stimulant of GIP hypersecretion, which is suggested as a cause of "sarcopenic obesity in elderly". In heart, aging is the known risk factor of HFpEF, of which typical characteristics is pathological cardiac hypertrophy induced by unknown cause(s). It remained uncertain whether any ectopic fat accumulation, such as cardiac steatosis may cause the aging-induced cardiac hypertrophy. Ceramide is one of the lipid metabolites that involves in apoptosis, inflammation, and stress responses, which are among the pathogenic components of heart failure. However, it remained unclear whether the ceramide may play any pathophysiological role in cardiac aging.

Purpose: We thus hypothesized whether cardiac aging may alter cardiac lipid metabolism and the GIP may play a regulatory role in the cardiac aging via modulating cardiac steatosis, particularly ceramide.

Methods: Mouse model of GIPR deficiency (GIPR-KO) was employed and cardiac evaluation of GIPR-KO and the age-matched wild type mice were performed.

Results: Aging (50w/o) induced GIP hypersecretion in control mice and their body and heart weight were 50% increased as compared to younger counterpart (10w/o). In contrast, the aging-induced increase rate in body and heart weight of GIPR-KO was significantly lower (22%). Aging also increased the circulating ketone bodies with increase in FGF21 expression in heart and, notably, there was no pathological increase in cardiac ceremide and oxidative stress with normal left-ventricular (LV) function (LVEF=82.2±1.8). In contrast, GIPR-KO exhibited pathological increase in cardiac ceramide without the elevation of the circulating ketone bodies. The younger GIPR-KO (10 w/o) exhibited normal left-ventricular (LV) function, however, the older mice (50 w/o) exhibited systolic LV dysfunction (LVEF=55.8±8.5) with increase in cardiac apoptosis and oxidative stress. Cardiac ceramide accumulation was increased in the aged normal mice, which was significantly higher in the aged GIPR-KO. Furthermore, GIPR-KO exhibited increase in cardiac fibrosis and oxidative stress, which were absent in the aged normal counterpart.

Conclusion: Aging increased circulating GIP level the leads to compensatory rise in the circulating ketone bodies without pathological increase in cardiac ceremide and related oxidative stress in heart. Loss of GIP signaling caused pathological increase in cardiac ceramide, leading to the aging-induced progression of systolic left-ventricular dysfunction. Collectively, we conclude that the aging-induced GIP hyperexcretion is essential for the aging-induced healthy cardiac remodeling by augmenting compensatory ketone body elevation.