Releasing Volume and Managing Ligand-Binding: the Resolution of TZD-Induced Cardiac Hypertrophy

Thiazolidinediones (TZDs), including rosiglitazone (Rosi) and pioglitazone (Pio), are PPAR\(_\gamma\) agonists used clinically to treat hyperglycemia associated with diabetes mellitus. Despite the evidence that TZDs prevent cardiac hypertrophy via an intrinsic cardiac pathway, it has been reported that TZDs caused cardiac hypertrophy in animal models, and increased risk of congestive heart failure in humans. Plasma volume expansion, a TZDs side effect, has been demonstrated to be mediated via renal PPAR\(_\gamma\) activation. Thus, we test whether TZD-induced cardiac hypertrophy is primarily due to volume overload through a PPAR\(_\gamma\) dependent pathway. We released TZD-induced volume overload by feeding mice diuretic furosemide (Furo), and examined the PPAR\(_\gamma\) dependency on either PPAR\(_\gamma\) haploinsufficient (\(Pparg^{+/+}\)) mice or ligand-binding deficient (\(Pparg^{L/+}\)) mice. We found that Furo effectively attenuated Rosi-induced volume overload, cardiac hypertrophy, apoptosis, and Erk1/2 activation without affecting glucose-lowering efficiency of Rosi. Although Furo blunted Rosi-induced upregulation of contractile and hormonal genes of heart, none of Rosi-reprogrammed metabolic genes was reversed by Furo. Thus, despite the direct effect of PPAR\(_\gamma\) activation on metabolic genes in heart, release of plasma volume ameliorated Rosi-induced cardiac hypertrophy, associated with attenuation of hypertrophic genes and signals. While the dosage was 4-fold higher of Rosi, we found that Pio cause volume overload and cardiac hypertrophy, and those were also blunted by Furo. Besides, \(Pparg^{L/+}\) but not \(Pparg^{+/+}\) is associated with attenuation of Rosi-induced volume overload and cardiac hypertrophy, suggesting that those effects require the intact ligand-binding ability of PPAR\(_\gamma\). Our work has identified the causative link of TZD-PPAR\(_\gamma\)-volume overload-cardiac hypertrophy axis, and provided the evidence that co-treatment with Furo and managing ligand-binding ability can prevent the cardiac side effect of TZDs.