Diuretics Prevent Thiazolidinedione-induced Cardiac Hypertrophy without Compromising Insulin-sensitizing Effects in Mice

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Type 2 diabetes mellitus is a chronic disease with worldwide prevalence, leading to the huge demand and cost of medicine usage. Thiazolidinediones (TZDs), including rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda), are one class of drugs used for the treatment of diabetes. TZDs are the high-affinity ligands targeting PPARγ, the gene which is critical for managing the metabolism in diverse tissues and cells. Thus, TZDs have potent effects on insulin-sensitizing thereby been used in clinic to improve the hyperglycemia of diabetic patient. However, concern of TZDs about cardiac side effect was increasing in recent years, which, in turn, shadows the benefits and limits the usage of this drug.

Another side effect of TZDs is plasma volume expansion. TZDs are known to induce the sodium reabsorption through the up-regulation of renal sodium transporters, contributing to the fluid retention and plasma volume expansion. Because the plasma volume expansion is a factor that may cause the cardiac hypertrophy, the side effect of TZDs on heart can be attributed to the increase of plasma volume. However, there is no direct evidence showing the causative role of plasma volume expansion in TZD-induced heart diseases. Thus, we asked whether the side effect of TZDs on heart could be solved by release of plasma volume expansion. To test this idea, we treated mice with diuretics furosemide (Furo) in combination with TZD for releasing plasma volume. We found the treatment of TZD caused the plasma volume expansion (Fig.1A), hemodilution, (Fig.1B) and cardiac hypertrophy (Fig.1C) in the mice. Co-treatment of Furo effectively reduced the TZD-induced plasma volume expansion, hemodilution, and cardiac hypertrophy (Figs.1A-C). The mice with Furo co-treatment also showed the attenuations of TZD-induced hypertrophic gene reprogramming, cardiomyocyte apoptosis, hypertrophy-related signal activation (Figs.2A and B), and left ventricular dysfunction. Importantly, TZD-mediated whole-body metabolic improvements were not affected by Furo co-treatment. We also evidenced the continuing treatment of Furo is needed, reflected by the reappearance of TZD-induced volume expansion and cardiac hypertrophy after stopping Furo administration for 1 week. In addition, other diuretics including spironolactone and thiazide were also effective to reduce TZD-induced volume expansion and cardiac hypertrophy. Thus, co-prescription of diuretics is advised for patients with TZD. We conclude that releasing plasma volume lowers side effects of TZD-induced volume expansion and cardiac events without compromising TZD’s actions whole-body insulin sensitivity. This is a strategy that could be immediately adopted without withdrawal of TZDs and testing new drugs that target PPARγ.
Figure 1. Diuretic furosemide inhibits TZD-induced volume expansion (A), hemodilution (B), and cardiac hypertrophy (C). Con, control; Rosi, rosiglitazone; Furo, furosemide.

Figure 2. Diuretic furosemide attenuates the TZD-induced phosphorylation of FAK and Erk1/2 (A) and nuclear translocation of phosphorylated Erk1/2. Con, control; Rosi, rosiglitazone; Furo, furosemide.