EFFECT OF PIOGLITAZONE ON INSULIN SIGNALING IN SKELETAL AND CARDIAC MUSCLES OF HIGH FAT-FED ZUCKER RATS.

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Thiazolidinediones (TZDs) improve glycemic control in patients with diabetes partly by improving glucose utilization by peripheral tissues and enhancing glucose uptake and insulin signaling in skeletal muscle. However, effects of TZDs on fat-induced derangements of insulin signaling are poorly understood. In this study, we investigated the effects of administration of pioglitazone (PIO) on phosphorylation and expression of key insulin signaling molecules in skeletal and cardiac muscles of high-fat fed fa/fa Zucker rats. **Methods:** Zucker rats were fed a high fat diet throughout the study. On study day 7, they were randomly assigned to a control group, 14-day PIO group, or a single-dose PIO group. Single-dose PIO received drug on the last study day via gavage (20 mg/kg). The 14-day PIO group received drug orally via admixture with chow. On study day 21, all animals were sacrificed within six hours after last dose of PIO. Blood and tissues (heart, soleus and plantaris muscle) were harvested and frozen for Western blot analysis of insulin receptor (InsR), ERK1,2, p38 MAPK, and Akt. **Results:** Chronic exposure in the 14-day PIO group, but not in acute group improved glycemia and reduced plasma insulin by 3-fold (P<0.05). In heart muscle, both single and 14-day PIO: a) decreased tyrosine phosphorylation of InsR and Akt on Ser⁴⁷³ by 30-60% (P<0.05), b) increased phosphorylation of p38 by 80% and ERK1,2 by 21-40% (P<0.05). In myocardium, both regimens of PIO increased Akt expression by 84-211% (P<0.05). In soleus muscle, acute and 14-day PIO reduced InsR phosphorylation by 39% (P>0.05) and 60% (P<0.05), respectively. In addition, any PIO exposure decreased ERK1,2 expression in soleus muscle. In plantaris muscle, compared to control, single dose PIO yielded 128-160% (P<0.05) increase in phosphorylation of ERK1,2, p38, and Akt. Moreover, 14-day PIO showed 180-350% (P<0.05) increase in phosphorylation. Any exposure to PIO decreased Akt expression by 22-35% (P<0.05). **Conclusion:** In insulin-resistant high-fat fed rats, administration of both single and 14-day PIO reduced InsR activation in cardiac and skeletal muscle. This was accompanied by activation of MAPKs in heart and plantaris, activation of Akt in plantaris, and no changes in MAPKs and Akt phosphorylation in soleus muscles. Therefore, the study suggests presence of differential effects of PIO on insulin signaling among different types of striated muscles. The results also demonstrate the effects of acute PIO on muscle insulin signaling without drug effects on hyperglycemia and insulinemia.