Pioglitazone Improves Insulin Resistance and atherosclerosis by both Adiponectin Dependent and Independent Pathways

Naoto Kubota,[1] Tetsuya Kubota,[1] Yasuo Terauchi,[2] Toshimasa Yamauchi,[1] Kohjiro Ueki,[1] Kazuyuki Tobe,[1] and Takashi Kadowaki,[1]
([1] Department of Metabolic Diseases, University of Tokyo, [2] Department of Diabetes and Endocrinology Yokohama City University)

Thiazolidinediones (TZDs) have been shown to upregulate adiponectin expression in white adipose tissue and plasma adiponectin levels, which has anti-diabetic and anti-atherosclerotic effects. It remains unclear, however, whether adiponectin is causally involved in the amelioration of insulin resistance and prevention of development of atherosclerosis. To address these issues, we used adiponectin-deficient (*adipo*$^{-/-}$) mice. We generated *adipo*$^{-/-}$ob/ob mice and found that the absence of adiponectin had no effect on either the obesity or the diabetic phenotype of these mice. After 10 mg/kg pioglitazone, TZD, treatment, the insulin resistance and diabetes of ob/ob mice improved significantly and these improvements were accompanied by significant upregulation of serum adiponectin levels, but insulin resistance and diabetes did not improve in the *adipo*$^{-/-}$ob/ob mice. Interestingly, the *adipo*$^{-/-}$ob/ob mice displayed a significant amelioration of insulin resistance and diabetes after 30 mg/kg pioglitazone treatment, similar to the improvements seen in ob/ob mice. We then investigated whether pioglitazone is capable of protecting neointima formation in response to cuff injury. The *adipo*$^{-/-}$ mice showed more cuff-induced neointima formation than the wild-type mice. After 3 weeks of pioglitazone treatment, the intimal thickness became significantly smaller in the wild-type mice with the upregulation of serum adiponectin levels, but was unchanged in the *adipo*$^{-/-}$ mice. The intimal thickness of the wild-type and *adipo*$^{-/-}$ mice, however, became significantly smaller after 8 weeks of pioglitazone treatment, but was indistinguishable between the two groups. Taken together, pioglitazone-induced amelioration of insulin resistance and suppression of atherosclerosis may occur both dependently and independently of adiponectin.