A small antidiabetic molecule prevents lipid induced insulin resistance through PPARγ dependent and independent pathways

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Prevalence of obesity induced diabetes has been dramatically increased over the past decades to an estimated number of 400 million people over the world. Oversupply of lipid that causes excessive deposition of intracellular fat in insulin target tissues is the most important factor for this insidious disease. Except TZDs there is practically no drug which addresses lipid induced defects responsible for Type 2 diabetes (T2D). TZDs are PPARγ ligands, they activate PPARγ and being a transcription factor it expresses genes related to insulin sensitization. We lost this remarkably advantageous drug because of its adverse side effects and toxicities. We prepared a peroxy Vanadate molecule with 3, 5 dimethylpyrazole (dmp) henceforth referred as dmp, it is toxicity free, soluble in water and stable at room temperature. Its primary effect is on lipid induced insulin resistance of adipose tissue and skeletal muscle cells. dmp dramatically changes the inflammation of

adipose tissue which include increase in the number of pre and mature adipocytes, decline of atrophied adipocytes, increased uptake of free fatty acids and elevation of glucose uptake by adipose tissue and skeletal muscle from HFD and db/db mice. These results indicate dmp's role as insulin sensitizer which they perform through PPARγ upregulation which remains suppressed in inflamed adipose tissue of HFD mice. PPARγ does not act directly for such improvement, but through the increase of adiponectin, CD36 and AP2 gene expressions. Besides PPARγ dependent effects, dmp also markedly reduced Fetuin A expression which is one of the important players in adipocytes inflammation. In addition, dmp protects mitochondrial damage due to excess lipid and stimulated Ampk activation in skeletal muscle cells. Taken together, dmp has an overall effect in preventing lipid induced insulin resistance in two major insulin target tissues.

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