Glycomics & Lipidomics

Extended Abstract

PPARs and their role in diabetic dyslipidaemia

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Abstract

Type 2 diabetes (T2D) is often associated with metabolic syndrome that is characterised by a peculiar dyslipidaemia comprising of elevated serum triglyceride levels in association with low HDL-Cholesterol levels (HDL-C). This disordered metabolic state leads to a build up of fatty acids in the liver and skeletal muscles, making these tissues resistant to the effects of insulin. The initial response of the body to insulin resistance is to increase insulin production that is effected by the beta cells of pancreas. Eventually, the beta cells are overwhelmed and can no longer produce enough insulin to maintain normoglycaemia, leading to the development of T2D. Peroxisome proliferator activated receptors (PPARs) are nuclear receptors that act as transcription regulators of various genes involved in energy metabolism. PPAR α and γ are the most studied and their agonists have been in use to treat both, T2D and dyslipidaemia. These agents have shown positive effects on multiple surrogate markers of cardiovascular disease. Furthermore, more recently, these agents have also demonstrated beneficial effects on hard clinical end points such as retinopathy as in the FIELD study. Although these metabolic benefits of PPAR agonists are mainly mediated through their genomic effects, our work has shown that some effects are potentially mediated through non-genomic effects as well. This is particularly well demonstrated in the enucleate platelet. We not only demonstrated the prescence of PPAR receptors in human platelets, but also that activating them has the potential to alter platelet aggregation and activation.

Diabetes mellitus is a chronic, lifelong condition that increases the body's blood glucose levels. There are three major types of diabetes namely Type 1 diabetes, Type 2 diabetes and gestational diabetes. Type 1 diabetes (insulin dependent) occurs when the body's immune system affects or kills the beta cells of the pancreas. PPAR agonists are drugs which activate peroxisome proliferator-activated receptor. Each isoform controls different activities. Agents that activate individual PPARs have different effects. They are used for treating the symptoms of Diabetes by lowering the triglycerides and blood sugar. PPAR agonists are ligand-regulated transcription factors that control gene expression by binding to specific response elements (PPREs) which is present within promoters. They are indicated for cholesterol disorders and disorders characterised by high triglyceride levels. PPAR-alpha, is produced in the skeletal muscles and the liver, where it is involved in the body's breakdown and transport of fatty acids. PPAR-alpha play a vital role in reducing inflammation both in the vascular wall and the liver. PPARs are effective in treating diabetes by lowering the triglycerides and blood glucose levels. PPARα agonists are used for treating dyslipidemia especially low HDL cholesterol and increased triglyceride levels. It is also effective in reducing cardiovascular problems. PPAR agonists are used for treating type 2 diabetes. PPAR gamma agonists regulates thefatty acid catabolism and energy uncoupling which in turn decreases the triglyceride stores and enhances the cardiac contractility. The activation of PPAR in the liver suppresses the hepaticglucose output which is responsible for improved glucose homeostasis.

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