

## Editorial

# Peroxisome Proliferator-Activated Receptors (PPARs) – The New Frontiers in the Treatment of Cardiovascular Diseases

## Introduction

Peroxisome Proliferator-Activated Receptors (PPARs) are nuclear hormone receptors that belong to the steroid/thyroid/retinoid superfamily of receptors<sup>1</sup>. PPARs form heterodimers with the Retinoid-X Receptors (RXRs) to form PPAR/RXR dimers that bind to a peroxisome proliferators-response element (PPRE)<sup>2</sup>, a DNA-specific sequence of which many types exist. This binding activates a change in gene transcription. There are three different PPAR isoforms: alpha, beta/delta and gamma which vary in their affinity to ligands, distribution throughout the body, and cofactor proteins they bind to. Each isoform has distinct properties and when activated stimulates the expression of genes involved in energy homeostasis, specifically the metabolism of glucose and fatty acids<sup>3</sup>. Ever since the recognition of their importance, vigorous research has led to uncovering a plethora of effects that they impact. In many clinical studies, they have been tested and proven to provide benefits in a wide array of cardiovascular diseases including but not limited to obesity, diabetes, atherosclerosis, and have been found useful to improve health and wellness. Some of them have even been used by muscle builders as a means to developing muscle mass. This article examines these receptors, their characteristics, the ligands that act on

them and how the ligands are being used to clinical advantage.

PPAR $\alpha$  activation increases the expression of lipoprotein lipase and apolipoprotein A-V (apoA-V) while simultaneously decreasing expression of apoC-III in the liver, which decreases VLDL particles and lowering plasma triglycerides<sup>2</sup>. These changes liberate fatty acids, allowing them to either be oxidized or stored. Thus, PPAR $\alpha$  agonists may therefore be beneficial in aiding fat loss. Unlike PPAR $\alpha$ , the exact functions of PPAR $\beta/\delta$  are still being researched, though in obese animals, it appears to decrease adiposity. Some opine that PPAR $\beta/\delta$  may serve as a "back-up" to PPAR $\alpha$  or have more specific actions in skeletal muscle than PPAR $\alpha$  does<sup>4</sup>.

PPAR $\gamma$  is involved in the storage of fatty acids and its activation can either increase or decrease the transcription of genes and enzymes involved in insulin sensitivity and adipogenesis, adipocyte differentiation, cell proliferation, and the inflammatory process<sup>5</sup>. All of these effects play a role in obesity and metabolic syndrome X (abdominal obesity, insulin resistance, and elevated blood pressure). Activation of PPAR $\gamma$  decreases insulin resistance, hence, the prototype compounds, the thiazolidinediones (TZDs) are known as classical anti-diabetic drugs

and have been used to treat type-2 diabetes though hepatotoxicity, sodium and water retention due to their use have limited their use<sup>6</sup>.

### **Pharmaceutical Drugs Targeting PPAR Fibrates and Cholesterol Levels**

Fibrates (fibric acid derivatives) are cholesterol-lowering drugs that work by decreasing the amount of circulating plasma cholesterol and triglycerides. Most fibrates also increase HDL levels and have been used by body builders because of its action as fatty acid-partitioning drugs, i.e. more fat makes their way to muscle and liver rather than fat tissue. Two fibrates that have been examined to a great extent are bezafibrate and gemfibrozil. The two studies most commonly referenced with regards to bezafibrate are the *Bezafibrate Coronary Atherosclerosis Intervention Trial* (BECAIT) study<sup>7</sup> and the *Bezafibrate Infarction Prevention* (BIP) study<sup>8</sup>. Both studies, involving post-myocardial infarction patients, demonstrated that bezafibrate decreased plasma fibrinogen levels, plasma cholesterol and triglyceride levels, and increased HDL levels leading to the conclusion that bezafibrate treatment is a safe and effective way to reduce plasma triglyceride levels and increase HDL levels.

Gemfibrozil, like bezafibrate, has been shown to decrease cholesterol and plasma triglyceride levels while increasing HDL levels and as demonstrated in *Helsinki Heart Study* (HHS)<sup>9</sup>, gemfibrozil reduced the risk of CHD by 34%. The *Veterans Affairs High-Density Cholesterol Intervention Trial* (VA-HIT) found similar results<sup>10</sup>.

### **PPAR $\gamma$ activation, Insulin Resistance and Type II Diabetes**

Thiazolidinediones (TZDs) are prototype PPAR $\gamma$  ligands (a.k.a. insulin sensitizers) known for their specific use in the management of Type II diabetes on account of their effect on activation of PPAR $\gamma$  and

decreased insulin resistance. Two examples of TZDs are troglitazone and pioglitazone. The Troglitazone Study Group<sup>11</sup> involving 330 patients found troglitazone to decrease plasma FFA levels, fasting plasma glucose, triglycerides, and fasting plasma insulin levels in type 2 diabetics. Pioglitazone has been shown to produce similar effects as troglitazone, except that pioglitazone caused these changes without affecting fasting or glucose-stimulated insulin levels<sup>12</sup>.

### **Supplements Targeting PPAR (Lignans and Fatty Acids)**

Due to the potential side effects associated with the current pharmaceutical drugs that target PPAR receptors, there is a search for safe alternatives. Current research is being done with various fatty acids and lignans - molecules that combine with a receptor or another entity acting as an "activator", to measure their ability to activate PPAR receptors. **Sesamin** is a naturally-occurring lignan found in sesame seeds and oil and has been shown to be a potent PPAR $\alpha$  agonist increasing fat oxidation in mitochondria and peroxisomes by increasing the expression of enzymes involved in  $\beta$ -oxidation of fatty acids<sup>13</sup> thus ensuring that less fat is esterified in the liver and thus less fat is stored in adipose tissue.

**Conjugated Linoleic Acid (CLA)** is a PPAR $\gamma$  antagonist that causes attenuation of fat cell differentiation. Supplementation with CLA has been shown to decrease adipocyte number and size<sup>14</sup>. It is available as a supplement and is a mix of isomers of linoleic acid (commercially sold as a 50:50 mix of cis-9, trans-11 and trans-10, cis-12 isomers). Studies done on humans have shown decreased body fat and/or increased lean mass (though results are mixed).

### **Future Research**

There is a strong potential for using PPAR ligands in the treatment of obesity, diabetes, atherosclerosis. Currently, human research is

being done on synthesized pharmaceutical drugs, which while effective in treating insulin resistance and elevated plasma triglycerides carry side effects with them. Like all pharmaceutical drugs, the costs versus benefits must be examined. The new wave of fatty acids and lignans that have been shown to be PPAR ligands are only in an infantile stage and with the exception of CLA, few human studies have been completed on these substances. Much more research needs to be done on these compounds in humans to examine their full beneficial and side effects. With obesity and type II diabetes becoming more and more prevalent, PPAR ligands are fast becoming the next hot topic in human research. While the ideal way to treat and prevent these conditions from occurring is consistent diet and exercise, the average individual especially those in affluent societies and/or lifestyles is suffering from these diseases is sedentary and not willing to put forth the effort needed to make lifestyle changes to correct the diseases. With this in mind, PPAR agonists may be the answer for them.

## References

- Keller JM, Collet P, Bianchi A, Huin C, Boullaud-Kremarik P, Becuwe P, Schohn H, Domenjoud L, Dauca M. Implications of peroxisome proliferator-activated receptors (PPARs) in development, cell life status and disease. *Int J Dev Biol.* 2000; 44(5): 429-442
- Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes.* 2005; 54(8): 2460-2470.
- Blaschke F, Takata Y, Caglayan E, Law RE, Hsueh WA. Obesity, peroxisome proliferator-activated receptor, and atherosclerosis in type 2 diabetes. *Arterioscler Thromb Vasc Biol.* 2006; 26(1):28-40.
- Tenenbaum A, Motro M, Fisman EZ. Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons. *Cardiovasc Diabetol.* 2005;16: 4-14.
- Kodera Y, Takeyama K, Murayama A, Suzawa M, Masuhiro Y, Kato S. Ligand type-specific interactions of peroxisome proliferator-activated receptor with transcriptional coactivators. *J. Biol. Chem.* 2000; 275: 33201-33204.
- Guo L, Tabrizchi R. Peroxisome proliferator-activated receptor gamma as a drug target in the pathogenesis of insulin resistance. *Pharmacol Ther.* 2006; 111(1): 145-173
- de Faire U, Ericsson CG, Grip L, Nilsson J, Svane B, Hamsten A. Secondary preventive potential of lipid-lowering drugs: the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *Eur Heart J* 1996; 17: 37 -42.
- The BIP Study Group: Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) Study. *Circulation*, 2000; 102: 21-27.
- Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; 317: 1237 -1245.
- Rubins HB, Rubins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*, 1999; 341: 410-418,
- Kumar S, Boulton AJ, Beck-Nielsen H, Berthezene F, Muggeo M, Persson B, Spinass GA, Donoghue S, Lettis S, Stewart-Long P. Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients: Troglitazone Study Group. *Diabetologia* 39: 701 -709,1996.
- Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino L, DeFronzo RA. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 2001; 24: 710 -719.
- Sirato-Yasumoto S, Katsuta M, Okuyama Y, et al. Effect of sesame seeds rich in sesamin and sesamol on fatty acid oxidation in rat liver. *J Agric Food Chem*, 2001; 49(5): 2647-2651.
- Larsen TM, Toubro S, Astrup A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res.* 2003; 44(12):2234-2241.

### Adebayo Oyekan

Professor and Director,  
Center for Cardiovascular Diseases  
College of Pharmacy and Health  
Sciences, Texas Southern University  
3100 Cleburne Avenue, Houston, TX  
77004,

**Email:** oyekan\_ao@tsu.edu