# PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPAR): A POTENTIAL STRATEGY TO COMBAT LIPOTOXIC HEART DISEASE

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## INTRODUCTION

**Obesity has been increasing dramatically in developed countries, which portends a higher incidence of cardiovascular risk factors such as insulin resistance, type 2 diabetes and hypertension. Accumulating evidence shows that the occurrence of heart disease in obesity is associated with the systemic dysregulation of lipid metabolism and not necessarily with hypertension and coronary artery disease. The impaired lipid metabolism may lead to cardiac lipid accumulation or "lipotoxic heart disease."1 This is also encountered in diabetic cardiomyopathy and in late stages of heart failure when global cardiac energy production is impaired. The accumulation of excess lipids has been known to cause cell dysfunction and/or cell death in non-adipose tissues such as the pancreas, although it is unknown whether a direct link between lipid accumulation and cell death occurs in the heart. Nevertheless, prevention or antagonism of cardiac lipid accumulation may serve as an adjunctive therapy for a variety of heart disorders that are accompanied by metabolic derangement.**

## MECHANISMS OF LIPOTOXIC HEART DISEASE

Normally, fat$_{ty}$ acid (FA) supply is tightly coupled to need in non-adipose cells, leaving little or no unoxidized FAs in these cells. In pathological states such as obesi$_{ty}$ or overnutrition, circulating FA levels increase and thus oversupply FAs to non-adipose cells. After entering cells, FAs are esterified to fatty acyl-CoAs and then transported across the mitochondrial membrane to undergo P-oxidation, producing acetyl CoA that enters the tricarboxylic acid cycle and yields ATP. If FA overload is imposed and/or FA utilization is suppressed or impaired, the faery acyl-CoAs can accumulate in the cytoplasm. These excess fatty acyl-CoAs will be diverted to synthesize triglycerides (TG), which are relatively inert and keep fatty acyl-CoAs away from pathways leading to apoprosis. When the content of intracellular fatty acyl-CoAs exceeds the TG storage capacity, which is limited in cardiac myocytes, fatty acyl-CoAs enter nonoxidative pathways such as ceramide synthesis. Ceramide has long been implicated in FA-induced apoptosis in non-adipose cells and could predictably result in loss of cardiac function. The accumulated acyl-CoAs also disrupt the insulin-signaling cascade that normally causes movement of glucose transporter 4 to the cell surface, resulting in impaired glucose uptake and cellular insulin resistance. The fares of fatty acyl-CoAs in cardiomyocyres are summarized in Figure 1.

## KEY ROLE OF PPARS IN CARDIAC LIPID METABOLISM

It has been well established chat FA metabolism is transcriptionally regulated by peroxisome proliferator-activared receptors (PPARs), members of the ligand-activated nuclear receptor superfamily.2 PPAR isoforms heterodimerize with the retinoid-X receptor (RXR) for binding to a conserved specific DNA sequence in the promoters of PPAR target genes and then activate transcription. To dare, three PPAR isoforms - a., PIS and y have been identified with specific tissue distribution; PPARa. and Bio are abundantly expressed in cardiac myocytes. Activation of PPAR transcriptional complexes occurs via binding of ligands, including both naturally occurring long-chain FAs and synthetic compounds such as the fibrate class of hypolipidemic drugs. In the heart, activation of PPARa. and PIS increases the expression of genes involved in cellular FA uptake as well as mitochondrial and peroxisomal B-oxidation,3 thus creating a positive feedback loop to handle the normal flow of intracellular FAs.

The important role of PPARa. and /8 in cardiac physiology has been illustrated in generically engineered mice. Heare-restricted PPARPlo knockout mice exhibit a considerable reduction of FA oxidative capaci$_{ty}$ and undergo progressive accumulation of neutral lipids in the hean.4 Similarly, systemic PPARa. knockout mice have lower constitutive cardiac expression of FA oxidative enzymes and exhibit age-dependent histological abnormalities such as contraction band necrosis and myocardial fibrosis when compared with wild-type controls.5 In the fasting state, stored triglycerides in adipose tissue are hydrolyzed to release FAs that are taken up by the liver, heart or other tissues to yield ATP. However, this

fasting-induced increase of FA utilization is completely abolished in PPARa knockout mice and is accompanied by myocardial lipid accumulation.6 Whether PPAR-y plays a physiologic role in the heart is still a matter for debate, but PPARy activity in skeletal muscle and adipose tissue may impact che function of myocardial PPARa and /3/0 through the effects of reducing circulating FA levels.

## INVOLVEMENT OF PPARS IN CARDIAC LIPOTOXICITY

As shown in Figure 1, cardiac lipotoxicity is thought to result from cwo different sicuacions: oversupply of FA to the heart or impairment of FA utilization. The first situation is frequently encountered in obesity, hyperlipidemia, high-fat diet and diabetes mellicus, while impaired FA ucilization is mainly seen in aging, hypertrophied or failing hearts. Through proton magnetic resonance spectroscopy, Petersen et al. showed that the elderly exhibit increased fat accumulation in muscle due to reduced mitochondrial oxidative activi cy.[7] Moreover, healthy, young, lean but insulin-resistant offspring of patiencs with type 2 diabetes have 80% higher intramyocellular lipid content when compared to insulin-sensitive controls. These studies beg the quesrion as ro whether the incidence of lipotoxic disease involves an impaired PPAR regulacory pathway due co ics critical role in lipid metabolism. Indeed, evidence shows that down-regulation of FA oxidative enzymes and their transcription faccor, PPARa, is the main reason for intracellular lipid accumulation in hearts from obese rats and resulrs in marked apopcosis and contractile dysfunction.[8,9] During cardiac hypertrophy and heart failure, reduced FA oxidation (FAO) rates result in lipid accumulation. This metabolic derangement is mediated, at least in part, through the down-regulation of the PPARa signaling pathway as the expression of PPARa, RXRa, and the PPAR interacting protein PGC-1 is reduced

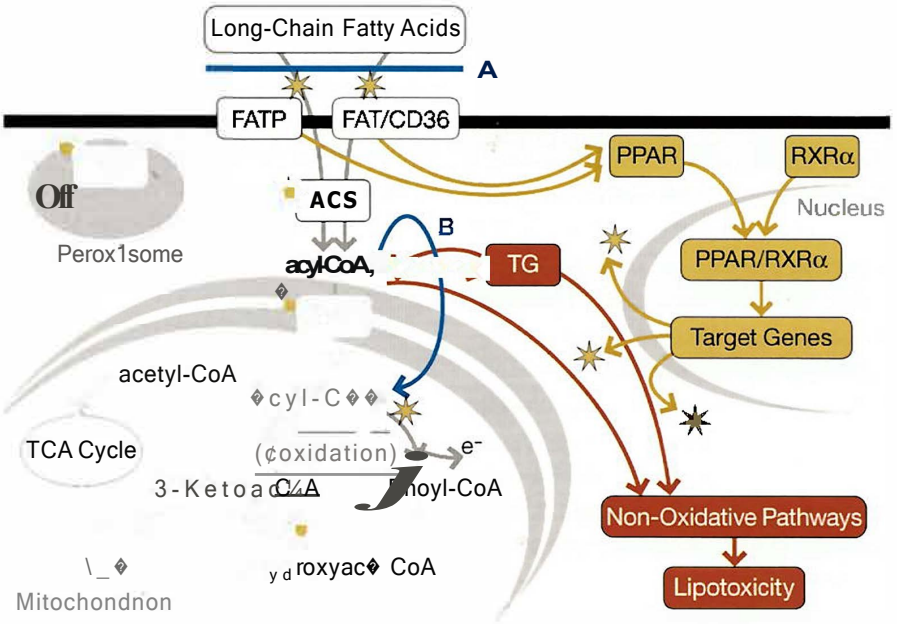


**Figure 1.** Schematic mechanisms of lipotoxic heart disease. In the normal state, most fatty acids (FAs) that are imported to the heart enter the mitochondrial -oxidation pathway. Oversupply of fatty acids or impaired fatty acid oxidative capacity leads to the accumulation of fatty acyl-CoAs in cardiac myocytes. A surplus of nonesterified FAs may increase the expression of FA oxidative enzymes {represented by gold stars) and thus normalize the intracellular FA level by serving as PPAR agonists. Surplus fatty acyl-CoAs can also be used to synthesize triglycerides. When the surplus intracellular FAs exceed the limit of these compensatory mechanisms, they will enter nonoxidative pathways such as ceramide synthesis and may contribute to lipotoxicity {indicated by red lines). Therefore, reducing the supply of long-chain FAs may keep the content of intracellular acyl-CoAs within the limits of oxidative capacity (A). Alternatively, increasing FA oxidation will divert the accumulated acyl-CoAs from nonoxidative pathways (B) and thus ameliorate lipotoxicity.
Abbreviations: ACO=acyl-CoA oxidase: ACS=acyl-CoA synthetase; CPT I=carnitine palmitoyltransferase I; FATP=fatty acid transportation protein; FAT/C036=fatty acid translocase CD36; PPAR=peroxisome proliferator-activated receptors: RXR=retinoid-X receptor; TCA cycle=tricarboxylic acid cycle; TG=triglycerides.

to fecal levels during cardiac hypertrophy.10 Collectively, discurbance of the normal PPAR signaling pathway is a hallmark signature for lipotoxic heart disease. Although the role of PPAR/31 O and y in lipotoxic heart disease has not been completely investigated, their importance in FA merabolism presumes that both also play key roles in the pathogenesis or treatmem of cardiac liporoxicicy.

## USE OF PPAR AGONISTS IN CARDIAC LIPOTOXICITY

Figure 1 suggests there are two potential strategies to prevem or ameliorate cardiac liporoxicity: reduce the supply of FAs to the heart and/or improve FAO in the heart. PPAR agonises might be ideal candidates co combat cardiac liporoxicicy by either increasing myocardial FAO capacity or reducing plasma FAs available to the heart through cheir actions in the liver, muscle and adipose tissue. In Zucker diabetic fatty rats, creatmem with the PPARy agonise, troglitazone, lowers myocardial T G and prevents apoptosis of cardiomyocytes and loss of cardiac function.[9] In ocher experimental models, administration of

PPARa agonises diminishes myocardial TG accumulation, inhibits production of inflammatory factors such as tumor necrosis factor, attenuates cardiac fibrosis and improves cardiac function.[11] Theoretically, PPARa activation could also induce the expression of FA importing proteins and thus increase FA uptake from the circulation. Therefore, the question of whether PPARa agonises induce or normalize an imbalance between the uptake and utilization of FAs requires further investigation.

There are no reports to dare of deteriorating cardiac function in humans treated with fibrates - synthetic PPARa agonises - despite widespread use to treat hyperlipidemia in patients with known cardiac disease, suggesting char PPARa agonises may provide a nee benefic co the cardiovascular system.

## CONCLUSION

PPARs cranscriptionally regulate every aspect of fatty acid metabolism. Therefore, developmenr of efficient and targeted PPAR agonists may serve as a novel strategy co combat heart disease complicated by myocyte lipid imbalance.

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