

**Review Article****Pharmaceutical and Biomedical Research****Peroxisome proliferator-activated receptors alpha and delta in diabetic cardiomyopathy****Mahkameh Soltani<sup>1</sup>, Ramin Ataee<sup>1,2\*</sup>**<sup>1</sup>Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran<sup>2</sup>Pharmaceutical Sciences Research Center, Hemoglobinopathy Institute, Mazandaran University of Medical Sciences, Sari, Iran*Received: Sep 7, 2015, Revised: Sep 26, 2015, Accepted: Nov 20, 2015***Abstract**

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors comprising three isoforms termed alpha, beta/delta and gamma. PPARs can modulate metabolic processes especially fatty acid (FA) metabolisms via exerting transcriptional control on activating genes involved in fuel utilization. Thus, they can exert positive role in controlling chronic diseases such as diabetes. As development of diabetes leads to functional and structural alterations at the myocardium termed diabetic cardiomyopathy (DCM), metabolic controller seems to be able to affect on cardiomyocytes. Herein, the role of PPAR $\alpha$ , and PPAR $\delta$ , is emerged and compared. This minireview discusses about these receptors in diabetes.

**Keywords:** Peroxisome proliferator-activated receptors (PPARs), metabolic processes, fatty acid (FA), diabetic cardiomyopathy (DCM), PPAR $\alpha$ , PPAR $\delta$

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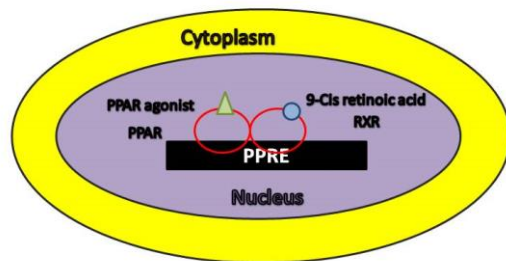
**Introduction**

As curve pertaining to morbidity and mortality of diabetes mellitus (DM) had positive slope in recent decades (1) and it is predicted to have 439 million diabetic patients in 2030 (2), more and more attention is paid to this issue. Additionally, myocardial dysfunctions such as diabetic cardiomyopathy (DCM) is more probable in DM patients compared to non-DMs (1). DCM is a pathological condition in which cardiomyocytes lose their potency to shift between different fuel substrate. Healthy heart uses long chain fatty acids (LCFA) providing 60-70% of ATP

requirement to power contraction (3-6), but cardiac substrate utilization is altered in the diabetic condition leading excessive use of FA oxidation up to 90-100% of the heart's ATP needs (5). As a result of metabolic derangements, myocardial dysfunction may appear. Complicated network regulating energy utilization and storage in myocardium is correlated with peroxisome proliferator-activated receptors (PPARs) (7,8). They are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily, including three isoforms termed as PPAR $\alpha$ , PPAR $\delta/\beta$

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(hereafter  $\delta$ ) and PPAR $\gamma$  (9). PPARs are activated by their selected ligands and form heterodimerize with retinoid X receptors (RXRs), respectively (10). Then the heterodimer binds to peroxisome proliferator response elements (PPREs), specific sequences in their target genes, and causes transcriptional switch (Fig. 1). Control of FA consumption and storage is considered as a prior outcome of activated PPRE (11). Current review highlights and compares the role of PPAR $\alpha$  and PPAR $\delta$  in fatty acid oxidation (FAO) and DCM.



**Figure 1** PPAR-RXR pathway: PPAR and RXRs coordinately regulate gene expression by means of forming heterodimers. The heterodimer binds to PPREs and exerts transcriptional effects.

#### *Pathophysiology of cardiomyopathy*

Heart is an organ with complicated cellular networks trying to maintain appropriate function. Despite all attempts, sometimes cardiomyocytes experience either revisable or unrevisable defaults leading to situation termed cardiomyopathy. Cardiomyopathy can occur as a result of mutation and extrinsic stimuli. Among 900 possible mutations affecting

cardiomyocytes 400 mutations are tolerated by 13 sarcomeric proteins including  $\beta$ -myosin heavy chain ( $\beta$ -MyHC),  $\alpha$ -cardiac actin, tropomyosin, and troponin (12). Mutation in troponin complex, an essential modulator of  $\text{Ca}^{2+}$ -stimulated actomyosin interaction or ATPase activity in the striated muscle, showed  $\text{Ca}^{2+}$ -desensitization and decreased maximal force in group of patients suffering Cardiomyopathies (13). Extrinsic stimuli are another reason for cardiomyopathy. Doxorubicin is an antineoplastic agent causing cardiomyocytes experience pathogeny. Doxorubicin not only is a potent agent causing mutation, but also directly affects the function of a variety of proteins (14). It changes the activity of the oxidation-sensitive enzyme creatine kinase in a cardiomyocyte culture model (15) and causes inhibition of carnitine palmitoyl transferase-1 dependent long chain fatty acid (palmitate) oxidation (16).

Regarding to the reason of cardiomyopathy, patients are generally divided in two groups termed as primary and secondary cardiomyopathies.

Primary cardiomyopathies includes disorders affecting the heart muscle, which have genetic, nongenetic, or acquired causes. Secondary cardiomyopathies expresses disorders that have myocardial damage because of systemic or multi-organ disease (17). There is also another characterization depending on the type of functional impairment of the

cardiomyocytes including three groups; dilated, hypertrophic, and restrictive cardiomyopathies (18). Restrictive cardiomyopathy and Arrhythmogenic cardiomyopathy are two other groups added to this classification during recent years (17).

#### *Heart fuel utilization and diabetes*

The heart uses various substrates for energy metabolism, including glucose and FAs. Translocation of glucose transporters GLUT1 and GLUT4 to the cell membrane regulates glucose uptake (19). As GLUT1 is responsible for continuous basal glucose transport and GLUT4 is regulated by insulin and metabolic stress, GLUT4 function is affected in abnormal conditions. Another energy source is FA that is used as oxidative substrate in the adult heart. In healthy adult heart, FA oxidation provides 60-70% of the heart's ATP requirements (3-5), but according to availability and physiological needs, this percentage shifts between LCFAs and glucose substrate. Fetal heart, pumping blood in a relatively hypoxic environment, derives energy largely from the oxygen-sparing catabolism of glucose (20). Moreover, in some pathological conditions glucose precedes FAs, such as patients tolerating cardiac hypertrophy. On the opposite point, there are situations in which FAs are totalitarian sources of energy like DCM condition.

GLUT4 trafficking is stimulated by two different patterns known as PI3 Kinase

dependent and independent pathways. PI3 Kinase dependent pathway is well documented as insulin sensitive pattern, but the correlation of IP3 Kinase independent pathway and insulin sensitivity is controversial (21). Thus, the dependent pattern is pointed as an effective factor in patients tolerating diabetes and insulin resistance.

Insulin binding to alpha subunit of insulin receptor (IR) is the first critical step in dependent pathway causing conformational changes in IR beta subunit leading to activation of IR intrinsic tyrosine kinase. The activated IR starts phosphorylation cascades via peptidase inhibitor 3 (PI3) Kinase phosphorylation. As a downstream event PI3 Kinase phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) and forms Phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 activate Pyruvate Dehydrogenase Kinase (PKD) 1 and mammalian target of rapamycin (mTOR) which both subsequently phosphorylates AKT/protein kinase B (PKB). Akt is made up of 3 subtypes named AKT1, AKT2 and AKT3. AKT2 continues the cascade by stimulating AKT Substrate of 160 KDa (AS160) which acts as GTPase Activating Protein (GAP) for Rab protein (22). At last phosphorylated Rab protein stimulates GLUT4 to be expressed on the plasma membrane (23).

All this processes occur in insulin sensitive cells, but diabetes and insulin resistance can block this pattern at initiating level. Another underlying

mechanism is related to the induction of inhibitory factors such as suppressors of cytokine signaling (SOCS). SOCS proteins block insulin signaling via competition with insulin receptor substrate (IRS)-1. Finally, increased activity of phosphatases which dephosphorylate intermediate signaling molecules can inhibit the insulin pathway (24). Taken together and as a result of insulin resistance GLUT4 trafficking is diminished and cardiomyocytes utilize FAs chiefly.

In diabetic cardiomyopathy, myocytes use LCFAs predominantly, therefore lipid metabolites are accumulated. Accumulation of lipid intermediates like diacylglycerol (DAG) is known to activate kinases such as PKC (25-28). As PKC is divided to three subgroups and each subgroup includes isotypes, they exert complicated effect in insulin pathway (29). Among isotypes, PKC $\theta$  and PKC $\epsilon$  clearly play a negative role in insulin pathway activation (30,31). PKC $\theta$  not only can phosphorylate IRS directly (32), but also through intermediates. As indirect role, PKC $\theta$  activates stress Kinases I $\kappa$ B $\alpha$ Kinase $\beta$  (IKK $\beta$ ) and c-Jun NH2-terminal Kinase (JNK) phosphorylating IRS and suppress insulin pathway (33). PKC $\epsilon$  can inhibit IRS via direct association with IRS (34) and also through direct phosphorylation (35). Another lipid intermediate produced through FAO pathway is ceramide. It can induce insulin resistance at the level of Akt inhibition (36,37). Pharmacological inhibition of ceramide synthesis has

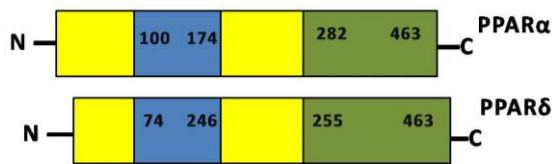
presented an effective role in preventing lipid-induced insulin resistance in rats. As ceramides are synthesized through denovo pathway in cardiomyocytes (38), pharmacological inhibition is required for this pathway. Denovo begins with the transfer of a serine residue onto a fatty acyl-CoA via serine palmitoyltransferase (SPT) (39) to form dihydrosphingosine which is converted to dihydroceramide via Ceramide synthase 4 (CerS4). On the other hand, CerS4 also uses preferential substrate that is provided via fatty acid elongase 6 (Elovl-6) to synthesize dihydroceramide. As the final step dihydroceramide changes to ceramide. Myriocin, a drug originated from Chinese traditional medication, is an example of pharmacologic ceramide inhibitor exerting selective inhibition on SPT leading to reduction of ceramide synthesis (39,41).

As a result of surplus FA consumption and blocked glucose pathway, it is plausible that cardiomyocytes experience lipotoxicity through oxidative stresses. Thus, it is important to find some metabolic controller in order to prevent probable risks.

#### *PPAR $\alpha$ , PPAR $\delta$ , two members of PPAR family*

PPARs include three subtypes termed PPAR $\alpha$ , PPAR $\delta$  and PPAR $\gamma$ . The subtypes have different characteristics including structure, tissue distribution, function and other features. From 1990 up to recent years PPAR $\gamma$  was discussed in detail, but less is known about other

subtypes, especially PPAR $\delta$ . PPAR structure is formed by slices including NH2 terminal, DNA binding domain (DBD), hinge region and C terminal. NH2 terminal mediates ligand-independent transcriptional activation, DBD indicates PPRE and C terminal encompasses ligand binding domain. Each slice has a unique pattern in PPAR $\alpha$  and PPAR $\delta$  (Fig. 2) (42).



**Figure 2** Schematic representation of PPAR $\alpha$  and PPAR $\delta$  protein domain. The numbers shown in the LBD and DBD refers to the number of amino-acids identified in PPAR $\alpha$  and PPAR $\delta$ .

As different structure leads to different function and PPARs distribution is correlated with their function, each subtype follows specific distribution pattern. PPAR $\alpha$  is mainly distributed in tissues with high capacity for fatty acid oxidation pathway such as heart, brown adipose tissue, skin, slow-twitch skeletal muscle and liver (43-45). PPAR $\delta$  is expressed predominantly in brain (46), adipose tissue, skin (45) and heart (47,48). Between these subtypes, PPAR $\alpha$  is highly presented in liver and there are only some traces of PPAR $\delta$  in hepatocytes (49). PPAR $\alpha$  is co-expressed with CYP4A enzymes in this tissue. It binds to PPRE in the P450A1 and 4A6 genes resulting in enzyme

induction. Despite PPAR $\alpha$ , PPAR $\delta$  seems to have no regulating effects on the expression of CYP4A or any other P450 enzyme (50). Considering P450 enzymes and especially CYP4A are responsible for many drugs and other substrates metabolization, it is important to recognize their common ligands. Fibrates are considered as the oldest PPAR $\alpha$  agonist. Natural carotenoid abundant in seafood can also stimulate PPAR $\alpha$  (51). AVE8134 is another PPAR $\alpha$  agonist newly found in 2012 and has amazing features (52). Unlike PPAR $\alpha$ , PPAR $\delta$  agonist is not well-known. GW50156 is an example of PPAR $\delta$  agonist employed in last decade. As GW50156 was plausible to contribute to carcinogenesis and also athlete abuse, now it does not seem to be a good choice(53).

Similarly to structure and tissue distribution PPRs functions can be analyzed. PPAR $\alpha$  agonist (54) reduces serum triglycerides (TG) and increases high density lipoprotein (HDL), but they also shows carcinogenic outcomes in rodents. Similarly PPAR $\delta$  activation causes reduction and elevation of TG and HDL in serum, respectively. This activation also triggers thermogenesis, weight loss and other metabolic possess (55,56). Glucose utilization and FAO, two main important sources of energy satisfying cellular metabolic demands, are strongly related to PPAR managements. Cardiomyocytes are very critical cells affected by PPARs function via metabolic controls (57).

*PPAR alpha and metabolism in cardiac cell*

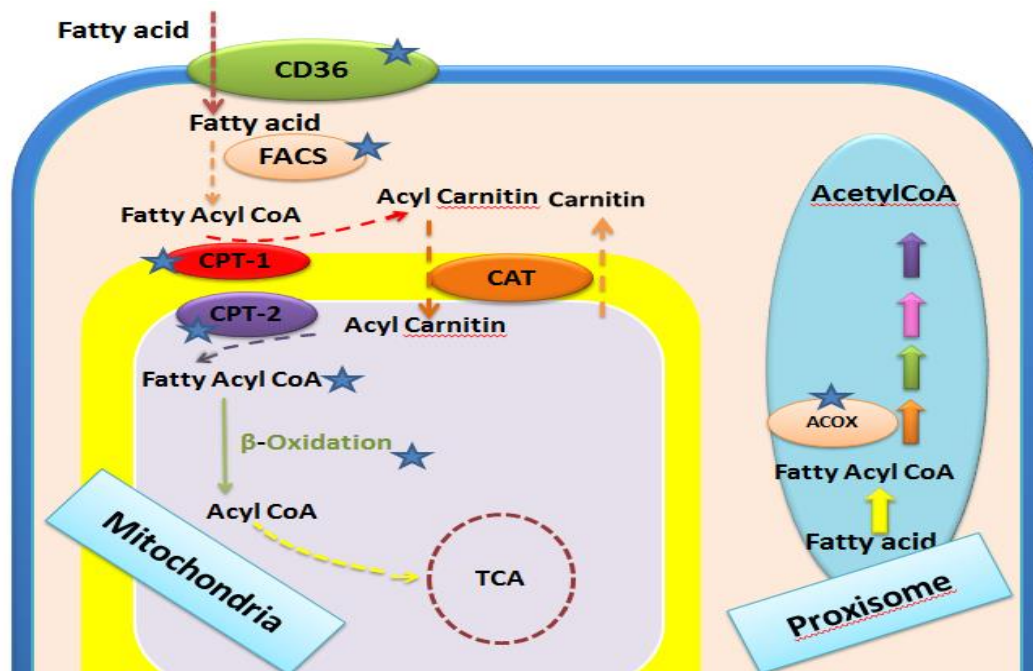
Studies have demonstrated a serious role for PPAR $\alpha$  by means of transcriptional control on genes involved in cardiac FA uptake and oxidation (58,59). In the heart, activation of PPAR $\alpha$  increases the expression of genes participating to cellular FA utilization pathway in three major steps in the including fatty acid transport and esterification (60,62), FA mitochondrial import (63), mitochondrial (62) and peroxisomal  $\beta$ -oxidation (Fig. 3) (64). Transporters and enzymes known to be regulated by PPAR $\alpha$  are indicated by a star. Abbreviations: (CPT I) carnitine palmitoyltransferase I; (CPT II) carnitine palmitoyltransferase II; (ACOX) acyl-CoA oxidase; (TCA) tricarboxylic acid.

Studies on PPAR $\alpha$  null mice also emerged an inability to pay for increased cardiac workloads and depression of cardiac contraction occurs. PPAR $\alpha$ -knockout mice display decreased cardiac FAO rates, but lipid uptake was presumably not affected, and cardiomyocyte lipid accumulation occurred. On the other hand, transgenic mice that over express PPAR $\alpha$  show an increase in the expression of genes encoding key enzymes involved in myocyte FA uptake and oxidation (65). Moreover, PPAR $\alpha$  activates pyruvate dehydrogenase kinase 4 (PKD4) (66). As PKD4 is responsible for phosphorylation of pyruvate

dehydrogenase (PDH), activated PKD4 leads to inhibition of PDH (67). PPAR $\alpha$  also exert a role in glycolysis via elevated FA metabolites. Increased amount of citrate level as an outcome of elevated FAO pathway contributes to the inhibition of phosphofructokinase (PFK)-I resulting in suppression of glycolysis (68)

*PPAR $\delta$  in cardiac cell*

PPAR $\delta$  effect FA uptake negatively. FAs derived from serum TG, through lipo-proteinlipase (LPL) activation, seem to be the major source of FAO pathway (69). PPAR $\delta$  can suppress the LPL-mediated uptake of TG-derived through upregulation of angiopoietin-like 4 (Angptl 4) (70). Angptl 4 is a secreted protein which inhibits the LPL (71). PPAR $\delta$  is able to avoid lipid accumulation by means of carnitine palmitoyltransferase (CPT) I. CPT1 is located within the mitochondrial outer membrane as a rate-limiting enzyme of mitochondrial-oxidation by controlling mitochondrial entry of long-chain fatty acids. Both PPAR $\alpha$  and PPAR $\delta$  activate CPT1, but the importance is behind the majority. CPT1 has three isoforms termed CPT1a, CPT1b, and CPT1c. CPT1b is the most predominant isoform and contributes 98% of total cardiac CPT1 activity. CPT1b is activated via PPAR $\delta$  (72), whereas PPAR $\alpha$  activate CPT1a (67). Surprisingly, PPAR gamma co-activator (PGC)-1 $\alpha$  acts as co-activator for PPAR $\delta$  in order to affect CPT1b (73). PGC-1 $\alpha$  also



**Figure 3** PPAR $\alpha$  targets in the cellular FAO pathway. Transporters and enzymes known to be regulated by PPAR $\alpha$  are indicated by a star. Abbreviations: (CPT I) carnitine palmitoyltransferase I; (CPT II) carnitine palmitoyltransferase II; (ACOX) acyl-CoA oxidase; (TCA) tricarboxylic acid.

accompanies PPAR $\delta$  for PKD4 activation (73).

### Conclusion

As cardiomyocytes become insulin resistance in diabetes, glucose pathway is not passed properly. Thus, cardiac cells utilize fatty acids excessively in order to respond their need, but elevated rate of FA consumption creates positive feedback for FOA pathway mainly through IRS phosphorylation. PPAR $\alpha$  activation help cardiomyocytes to greet more FA from out of the cell via CD36 and increases available FAs. In the opposite point, PPAR $\delta$  suppress FA LPL-dependent uptake by activating Angptl4. PPAR $\delta$  helps ATP production

via CPT1b. This transporter continues FOA pathway toward mitochondria for  $\beta$ -oxidation. Both PPAR $\alpha$  and PPAR $\delta$  activate PDK4. PDK4 inactivate Pyruvate Dehydrogenase (PDH) by means of phosphorylation. Thus, cardiomyocytes are forced to end glycolysis at aerobic point through lactate production.

### Conflict of interests

Nothing to declare.

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