**PPARγ agonist-induced alterations in Δ6-desaturase and stearoyl-CoA desaturase 1: Role of MEK/ERK1/2 pathway**

Negar Saliani, Masoud Darabi, Bahman Yousefi, Behzad Baradaran, Mahmoud Shekari Khani, Maryam Darabi, Maghsod Shaaker, Amir Mehdizadeh, Tahereh Naji, Mehrdad Hashemi

**METHODS:** HepG2 cells cultured in RPMI-1640 were exposed to the commonly used ERK1/2 pathway inhibitor PD98059 and PPARγ agonist, pioglitazone. Total RNA was isolated and reverse transcribed from treated cells. Changes in gene expression and metabolites ratio, as activity index for Δ6D and SCD1, were then determined using reverse transcription-polymerase chain reaction and gas liquid chromatography, respectively.

**RESULTS:** The expression of both Δ6D (P = 0.03) and SCD1 (P = 0.01) increased following PD98059 treatment, with a higher impact on SCD1 (24.5% vs 62.5%). Although pioglitazone increased the mRNA level (1.47 ± 0.10 vs 0.88 ± 0.02, P = 0.006) and activity index (1.40 ± 0.07 vs 0.79 ± 0.11, P < 0.001) of Δ6D, no such changes have been observed for SCD1 activity in pioglitazone-treated cells. SCD1 gene expression (+26.4%, P = 0.041) and activity index (+52.8%, P = 0.035) were significantly increased by MEK inhibition in the presence of pioglitazone, as compared with pioglitazone alone and control cells. However, the response of Δ6D expression and activity index to pioglitazone was unaffected by incubation with PD98059.

**CONCLUSION:** PPARγ and ERK1/2 signaling pathway affect differentially and may have inhibitory crosstalk effects on the genes expression of Δ6D and SCD1, and subsequently on their enzymatic activities.

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INTRODUCTION

Fatty acid desaturation is a lipid modification process that is critically important in multiple biological functions, such as cell membrane fluidity, signal transduction, differentiation, inflammatory responses and brain development\(^1\). Both the Δ6-desaturase (Δ6D) and stearoyl-CoA desaturase 1 (SCD1) are two important regulatory enzymes in hepatic de novo fatty acid synthesis. Activities of these enzymes provide essential precursors for structural cell components and bioactive metabolites such as prostaglandins\(^3\). Altered levels of both SCD1 activity\(^4\) and Δ6D activity\(^5\) have been reported in various human diseases.

The expressions of both enzymes are coordinately regulated and efficiently induced by the addition of thiazolidinediones (TZDs). TZDs are known as agonists of the gamma isof orm of the peroxisome proliferator-activated receptors (PPAR\(\gamma\)), a family of nuclear receptors regulating the expression of genes involved in fatty acid metabolism. Indeed, functional PPAR response elements in the promoter region of the Δ6D and SCD1 have been identified\(^6\).

Pioglitazone, a member of the TZD family, is widely used as an antidiabetic agent with glucose-lowering and lipid modifying effects in non-insulin-dependent diabetes mellitus\(^7\). Despite the increasing clinical use, the mechanisms by which pioglitazone exerts its effects are yet relatively unknown.

Alternatively, signaling pathways might modulate the activity of PPAR\(\gamma\) to regulate cellular fatty acid desaturation events. We have recently shown that fatty acid content of HepG2 cells is susceptible to inhibition of MEK/ERK1/2 pathway\(^8\). Exposure of cells to the ERK1/2 pathway inhibitor induced an increase in monounsaturated fatty acids (MUFA) and the fatty acid desaturation index. Consistent with these findings, the activity of PPAR\(\gamma\) has been reported to regulate cellular fatty acid de

MATERIALS AND METHODS

Materials

Cell culture materials, media, FBS and standard fatty acid methyl esters were obtained from Sigma Chemical Company (St. Louis, MO, United States). Pioglitazone and PD98059 were purchased from Cayman Chemical (Ann Arbor, MI, United States). HepG2 cell line was obtained from the Pasteur Institute Culture Collection in Tehran. The TRIzol reagent for RNA isolation was purchased from Invitrogen (Carlsbad, CA, United States). AccuPower RT PreMix for the first-strand cDNA synthesis was purchased from Bioneer (Daejeon, South Korea). All other chemicals used were of analytical grade.

Cell culture

HepG2 cells were grown in RPMI1640 containing 10% FBS, L-glutamine (2 mmol/L), penicillin (100 units/mL), and streptomycin (100 µg/mL) at 37 °C, 5% CO\(\text{2}\). The cells were seeded at a density of \(2.5 \times 10^4\)/well in a 6-well plate. After allowing the cells to attach overnight, the medium was replaced with fresh medium containing ± pioglitazone (20 µmol/L) and PD98059 (20 µmol/L). Following 48 h incubation, culture medium was removed; the cell monolayer was washed, and collected for gene expression study and cellular fatty acid measurement.

RT/PCR analysis

Total RNA was purified with TRIzol reagent. One µg of RNA was reverse-transcribed using the AccuPower cDNA kit as per the manufacturer’s instructions. Semiquantitation of the cDNA was performed by RT/PCR using the primer-dropping method according to a previous report\(^9\). Each reverse transcript (i.e., Δ6D and SCD1 cDNA) was amplified with β-actin as an internal control. Under standard conditions of PCR, all the test transcripts were amplified within their log linear phase. The primers used were: D9D: F (5’-CATATTCCCGAGCTTTGTGTT-3’), R (5’-AGGTTTTGATGACCTCCTGGAACA-3’) (150 bp); D6DF: (5’-CTGCCAACTGGTGGAAT-3’), R (5’-AAACACGTGCGGACTGT-3’) (94 bp), β-actin: F (5’-TGGACTTTCGAGCAAGAGAC-3’), R (5’-GAGGAGAGCTGGAAAGAGT-3’) (137 bp). For comparing the amount of PCR product between samples, a gel digitizing software, UVitec (version 11.01), was used for estimating the intensity of each band on the gel. Each experiment was repeated four times. The coefficients of variation (CV) were about 5%-8%.

Fatty acid analysis

Fatty acid methyl esters were extracted and analyzed for fatty acid composition, as described previously by us\(^10\). Briefly, fatty acid methyl ester derivatives formed from

Saliani N et al. PPAR\(\gamma\) and ERK1/2 effect on desaturases
Table 1 Effect of pioglitazone on the fatty acid composition of HepG2 human hepatic cells

|                | Control       | Pioglitazone | Pioglitazone + PD98059 |
|----------------|---------------|--------------|------------------------|
| 14:0 (myristic acid) | 2.01 ± 0.42   | 2.03 ± 0.35  | 1.77 ± 0.17             |
| 16:0 (palmitic acid) | 23.12 ± 1.24* | 23.26 ± 1.11* | 19.84 ± 1.21*          |
| 16:1 (palmitoleic acid) | 7.44 ± 1.11   | 9.60 ± 1.55  | 8.52 ± 1.45             |
| 18:0 (stearic acid) | 10.44 ± 1.29  | 11.12 ± 1.37 | 8.78 ± 1.14             |
| 18:1n 9 (oleic acid) | 38.72 ± 1.43  | 37.33 ± 0.80* | 44.94 ± 1.08*          |
| 18:2n 6 (linoleic acid) | 9.09 ± 0.27   | 6.18 ± 0.68* | 6.09 ± 0.56*            |
| 18:3n 3 (eicosapentaenoic acid) | 0.89 ± 0.13 | 0.72 ± 0.12  | 0.61 ± 0.12             |
| 20:4n 6 (arachidonic acid) | 7.19 ± 0.79   | 8.62 ± 0.58  | 8.85 ± 0.85             |
| 20:5n 3 (docosapentaenoic acid) | 0.42 ± 0.13 | 0.47 ± 0.21  | 0.14 ± 0.10             |
| 22:6n 3 (docosahexaenoic acid) | 0.68 ± 0.14   | 0.67 ± 0.10  | 0.46 ± 0.11             |
| Saturated fatty acids | 35.58 ± 1.29* | 36.41 ± 2.18* | 30.39 ± 2.05*          |
| Monounsaturated fatty acids | 46.16 ± 1.75* | 46.90 ± 2.24* | 53.46 ± 1.53*          |
| Polyunsaturated fatty acids | 18.27 ± 0.61  | 16.66 ± 1.44 | 16.15 ± 1.22             |

Cells were incubated with pioglitazone (20 µmol/L) and PD98059 (20 µmol/L) for 48 h. Lipid extracts were prepared and analyzed by gas liquid chromatography for a comprehensive fatty acid profile. The mean ± SD of 3 independent experiments done in duplicate are given. "P < 0.05 and "P < 0.01 (Tukey’s test, ‘u = 0.05). Detection limit was 0.05% of the total area.

RESULTS

To determine the effect of ERK1/2 MAPK pathway on Δ6D and SCD1, HepG2 cells were treated with PD98059. PD98059 significantly increased the expression levels of both Δ6D (P = 0.03) and SCD1 (P = 0.01). Our data also revealed that ERK1/2 deprivation had a higher impact on SCD1 expression than on Δ6D expression (24.5% vs 62.5%; Figure 1).

To determine the effect of PPARγ stimulation on Δ6D and SCD1 expression, HepG2 cells were treated with pioglitazone, a PPARγ agonist. Δ6D showed significant increase in mRNA level (1.47 ± 0.10 vs 0.88 ± 0.02, P = 0.006), whereas SCD1 expression did not significantly change (P = 0.47; Figure 1). We next determined the effect of the PPARγ agonist on fatty acid composition of HepG2 cells (Table 1). The ratios of arachidonic acid (20:4n-6)/linoleic acid (18:2n-6) and oleic acid (18:1n-9)/stearic acid (18:0) were calculated as indices of Δ6 fatty acid desaturase and SCD1 activity, respectively. Incubation with pioglitazone reduced 18:2n-6 levels (P = 0.001) and increased Δ6D activity index (1.40 ± 0.07 vs 0.79 ± 0.11; P < 0.001). However, no such change has been observed for SCD1 activity index in pioglitazone-treated cells (Figure 2).

Comparison of control with the combined drug condition showed a significant increase in the expression of both Δ6D (P = 0.02) and SCD1 (P = 0.04). The expression of Δ6D increased in comparison to the condition which was just treated with PD98059 (P = 0.032), but comparable to pioglitazone alone. The expression of SCD1 was more than the situation treated with pioglitazone alone (1.15 ± 0.15 vs 0.91 ± 0.20, P = 0.041, Figure 1). Consistent with data from gene expression analyses, MEK inhibition induced a significant increase in SCD1 activity index (+52.82%, P = 0.035), compared with pioglitazone-treated and control cells. These changes were coupled with significant alteration in fatty acid composition, including increased percentage of MUFA (P = 0.012) and reduced saturated fatty acids (SFA; P = 0.018). In addition, the response of Δ6D activity index to pioglitazone was unaffected by incubation with PD98059 when compared to cells incubated with pioglitazone alone (Figure 2).

DISCUSSION

The expression of Δ6D and SCD1 is regulated by complex environmental and hormonal factors.[19,20] Activities of these enzymes can affect several hepatic metabolic processes, such as glucose metabolism and membrane permeability, through modulation of cellular fat content. On the other hand, altered lipid content of hepatic cells makes a major contribution in the rate of de novo lipogenesis and inducing steatosis.[21] Abnormal lipid uptake or de novo lipogenesis has been reported in various types of hepatic disorders, which is characterized by increased production of bioactive lipids and an inflammatory response.[22] In a previous study, we have demonstrated that the fat composition of hepatocellular carcinoma
cell line HepG2 was affected by MEK/ERK1/2 signaling. We concluded that MEK/ERK1/2 kinase signaling serves to coordinate fatty acid metabolism in HepG2 cells. In the current study, the expression levels of Δ6D and SCD1 were increased in the presence of MEK inhibitor. These findings are consistent with our earlier report indicating increased 18:1n-9/18:0 and 20:4n-6/18:2n-6 ratios as indices of desaturase activity after inhibition of ERK1/2 signaling. Thus, these enzymatic activities may be under inhibitory control of ERK1/2 signaling. Presumptively, ERK1/2 modulates desaturases expression by implying several molecular mechanisms, including enhanced affinity of transcription factors, gene suppression through direct interaction with DNA, modulation of transcription factors, and MAPK-dependent attenuation of PPARγ transcriptional activity. Camp et al. demonstrated that activation of ERK1/2 in adipocytes abrogates both ligand-independent and ligand-dependent activities of PPARγ. Taken together, the regulation of desaturases expression by key transcription factors such as PPARγ could be modulated by ERK1/2 cascade.

PPARγ has been shown to be critically important in multiple biological functions. TZDs, high-affinity synthetic PPARγ agonists, mediate the transcription of PPARγ-dependent genes by binding to PPARs as a ligand. Herein, we have shown that treatment of HepG2 cells with pioglitazone, a PPARγ agonist, increased both Δ6D mRNA expression and Δ6D activity index whereas had no effect on SCD1. These results led us to speculate that an additional mechanism was at work. Remarkably, it has been illustrated that PPARγ agonists not only can function in a PPARγ-dependent manner but also are capable of activating ERK1/2 pathway independently of PPARγ. Accordingly, Kempná et al. demonstrated that pioglitazone activates ERK1/2 MAPK pathway in NCI-H295R cells. Presumably, no changes in SCD1 expression could be attributed to equal and opposite effects of pioglitazone via PPARγ dependent and PPARγ independent mechanisms. In accordance with our results, the administration of pioglitazone to Zucker obese rats did not affect the mRNA level of SCD1. However, treatment of rats fed a high-sucrose diet with TZDs decreased significantly the hepatic SCD1 mRNA expression. In this context, TZDs have also been reported to significantly reduce Δ6D mRNA level. These contradictory findings might be due to differences in applying TZDs, types of cell lines, tissues and animal models.

Cotreatment of HepG2 cells with pioglitazone and ERK1/2 inhibitor PD98059 resulted in enhanced rather than additive or synergistic expression. It is of particular interest that activated ERK1/2 MAPK pathway via pioglitazone in a PPARγ independent manner could also occur without phosphorylation of upstream MEK. So, this underscores pioglitazone ability in activation of ERK1/2 MAPK pathway through other additional pathways. Accordingly, in presence of both PD98059 and pioglitazone the ERK1/2, which may be activated independently of MEK, could prevent synergistic increase of SCD1 expression, and subsequently SCD1 activity. Studies in humans have reported that increased expression of SCD1 may protect against insulin resistance. The fact that a combination treatment using the PPARγ agonist pioglitazone and the MEK/ERK1/2 inhibitor was more efficient at inducing SCD1 than pioglitazone alone suggests that TZDs along with MEK/ERK1/2 inhibition may be therapeutically beneficial for insulin resistance.
resistance related to type 2 diabetic patients.

To our knowledge, this study is the first study to examine the combined effect of PPARγ agonist and ERK1/2 blockade on the gene expression and derived activity index of fatty acid desaturases. The regulatory effects were simultaneously analyzed by studying the expression and endogenous activity index of both ∆6D and SCD1, which made it possible to identify similarities and differences. It remained to be clarified what mechanism is involved in PPARγ and ERK1/2 MAPK crosstalk in the regulation of fatty acid desaturases in the liver cells.

In conclusion, our study showed that PPARγ and ERK1/2 MAPK signaling pathway affect the gene expression and activity of ∆6D and SCD1 in hepatic HepG2 cells. Furthermore, a possible inhibitory crosstalk between PPARγ and ERK1/2 MAPK signaling pathway may have different affects on ∆6D and SCD1 genes expression, and subsequently on their enzymatic activities.

**REFERENCES**

1. Jump DB. Fatty acid regulation of hepatic lipid metabolism. *Curr Opin Clin Nutr Metab Care* 2011;14: 115-120 [PMID: 21178610 DOI: 10.1097/MCO.0b013e328342991c]
2. Liu X, Strable MS, Ntambi JM. Stearoyl CoA desaturase 1: role in cellular inflammation and stress. *Adv Nutr* 2011;2: 15-22 [PMID: 22211186 DOI: 10.3945/an.110.000125]
3. Fevre C, Bellenger S, Pierre AS, Minville M, Bellenger J, Gres-Tj, Rialland M, Narce M, Tessier C. The metabolic cascade leading to eicosanoid precursors--desaturases, elongases, and phospholipases A2--is altered in Zucker fatty rats. *Biochim Biophys Acta* 2011;1811: 409-417 [PMID: 21172452 DOI: 10.1016/j.bbabio.2010.12.004]
4. Astarita G, Jung KM, Vasilevko V, Dipatrizio NV, Martin SK, Cribs DB, Head E, Cotman CW, Piomelli D. Elevated stearoyl-CoA desaturase in brains of patients with Alzheimer's disease. *PLoS One* 2011; 6: e24777 [PMID: 22064234 DOI: 10.1371/journal.pone.0024777]
5. Gutiérrez-Juárez B, Poció A, Mulas C, Ono H, Bhanot S, Mo-nia BP, Rossetti L. Critical role of stearoyl-CoA desaturase-1 (SCD1) in the onset of diet-induced hepatic insulin resistance. *J Clin Invest* 2006; 116: 1686-1695 [PMID: 16741579 DOI: 10.1172/JCI26991]
6. MacDonald ML, van Eck M, Hildebrand RB, Wong BW, Bissada N, Ruddle P, Kontush A, Hussein H, Pouladi MA, Campbell MJ, Fievet C, van Berkel TJ, Staelens B, McNamus BM, Hayden MR. Despite antiatherogenic metabolic characteristics, SCD1-deficient mice have increased inflammation and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2009; 29: 341-347 [PMID: 19005997 DOI: 10.1161/ATVHA.108.180933]
7. Liu Y, McNamara RK. Elevated Delta-6 desaturase (FADS2) gene expression in the prefrontal cortex of patients with bipolar disorder. *J Psychiatr Res* 2011; 45: 269-272 [PMID: 20615514 DOI: 10.1016/j.jpsychires.2010.06.010]
8. Tang C, Cho HP, Nakamura MT, Clarke SD. Regulation of human delta-6 desaturase gene transcription: identification of a functional direct repeat element. *J Lipid Res* 2003; 44: 686-695 [PMID: 12562861 DOI: 10.1194/jlr.M200195-JLR200]
9. Miller CW, Ntambi JM. Peroxisome proliferators induce mouse liver stearoyl-CoA desaturase 1 gene expression. *Proc Natl Acad Sci USA* 1996; 93: 9443-9448 [PMID: 8790349 DOI: 10.1073/pnas.93.18.9443]
10. Friedland SN, Leong A, Filion KB, Genest J, Lega IC, Mot-tillo S, Poirier P, Rech J, Eisenberg MJ. The cardiovascular effects of peroxisome proliferator-activated receptor agonists. *Ann Med* 2012; 44: 126-133 [PMID: 22209613 DOI: 10.1016/j.annmed.2011.08.025]
11. Yousefi B, Darabi M, Baradaran B, Khaniani M, Rahbani M, Darabi M, Fayozi S, Meh dizadeh A, Sali ani N, Shaaker M. Inhibition of MEK/ERK1/2 signaling affects the fatty acid composition of HepG2 human hepatic cell line. *BioImpacts* 2012; 2: 145-150 [DOI: 10.5681/bi.2012.019]
12. Mauvoisin D, Prévost M, Ducheix S, Arnaud MP, Mounier C. Key role of the ERK1/2 MAPK pathway in the transcriptional regulation of the Stearoyl-CoA Desaturase (SCD1) gene expression in response to leptin. *Mol Cell Endocrinol* 2010; 319: 116-128 [PMID: 20109524 DOI: 10.1016/j.mce.2010.01.027]
13. Kempan N, Hofer G, Mullis PE, Flick CE. Pimaglizone inhibits its androgen production in NCI-H295R cells by regulating gene expression of CYP17 and HSD3B2. *Mol Pharmacol* 2007; 71: 787-798 [PMID: 17138841 DOI: 10.1124/mol.106.026902]
14. Camp HS, Tafuri SR. Regulation of peroxisome proliferator-activated receptor gamma activity by mitogen-activated protein kinase. *J Biol Chem* 1997; 272: 10811-10816 [PMID: 9099735 DOI: 10.1074/jbc.272.10.10811]
15. Liu Y, Jandacek R, Rider T, Tso P, McNamara RK. Elevated delta-6 desaturase (FADS2) expression in the postmortem prefrontal cortex of schizophrenic patients: relationship with...
fatty acid composition. *Schizophr Res* 2009; 109: 113-120 [PMID: 19159854 DOI: 10.1016/j.schres.2008.12.027]

16 **Noori M**, Darabi M, Rahimipour A, Rahbani M, Abadi NA, Darabi M, Ghatrehsama K. Fatty acid composition of HDL phospholipids and coronary artery disease. *J Clin Lipidol* 2009; 3: 39-44 [PMID: 21291787 DOI: 10.1016/j.jacl.2008.11.010]

17 **Guillou H**, Martin PG, Pineau T. Transcriptional regulation of hepatic fatty acid metabolism. *Subcell Biochem* 2008; 49: 5-47 [PMID: 18751906 DOI: 10.1007/978-1-4020-8831-5_1]

18 **Ntambi JM**, Miyazaki M. Regulation of steroyl-CoA desaturases and role in metabolism. *Prog Lipid Res* 2004; 43: 91-104 [PMID: 14654809 DOI: 10.1016/S0163-7827(03)00039-0]

19 **Pachikian BD**, Essaghir A, Demoulin JB, Neyrinck AM, Catry E, De Backer FC, Dejeans N, Dewulf EM, Sohet FM, Portois L, Deldicque L, Molendi-Coste O, Leclercq IA, Francaux M, Carpentier YA, Foulfe F, Muccioli GG, Cani PD, Delzenne NM. Hepatic n-3 polyunsaturated fatty acid depletion promotes steatosis and insulin resistance in mice: genomic analysis of cellular targets. *PLoS One* 2011; 6: e25365 [PMID: 21853118 DOI: 10.1371/journal.pone.0025365]

20 **Bjermo H**, Risérus U. Role of hepatic desaturases in obesity-related metabolic disorders. *Curr Opin Clin Nutr Metab Care* 2010; 13: 703-708 [PMID: 20823776 DOI: 10.1097/MCO.0b013e3283cc4eb1]

21 **Hein GJ**, Bernasconi AM, Montanaro MA, Pellon-Maison M, Finarelli G, Chicco A, Lombardo YB, Brenner RR. Nuclear receptors and hepatic lipogenic enzyme response to a dyslipidemic sucrose-rich diet and its reversal by fish oil n-3 polyunsaturated fatty acids. *Am J Physiol Endocrinol Metab* 2010; 298: E429-E439 [PMID: 19952544 DOI: 10.1152/ajpendo.00513.2009]

22 **Kotronen A**, Seppänen-Laakso T, Westerbacka J, Kiviluoto T, Arola J, Ruskeeläppä AL, Oresic M, Yki-Järvinen H. Hepatic steroyl-CoA desaturase (SCD)-1 activity and diacylglycerol but not ceramide concentrations are increased in the nonalcoholic human fatty liver. *Diabetes* 2009; 58: 203-208 [PMID: 19592834 DOI: 10.2337/db08-1074]

23 **Hu S**, Xie Z, Onishi A, Yu X, Jiang L, Lin J, Rho HS, Woodard C, Wang H, Jeong JS, Long S, He X, Wade H, Blackshaw S, Qian J, Zhu H. Profiling the human protein-DNA interactome reveals ERK2 as a transcriptional repressor of interferon signaling. *Cell 2009; 139: 610-622 [PMID: 19879846 DOI: 10.1016/j.cell.2009.08.037]*

24 **Wang Y**, Botolin D, Xu J, Christian B, Mitchell E, Jayaprakasam B, Nair MG, Peters JM, Busik JV, Olson LK, Jump DB. Regulation of hepatic fatty acid elongase and desaturase expression in diabetes and obesity. *J Lipid Res* 2006; 47: 2028-2041 [PMID: 16790840 DOI: 10.1194/jlr.M600177-JLR200]

25 **Adams M**, Reginato MJ, Shao D, Lazar MA, Chatterjee VK. Transcriptional activation by peroxisome proliferator-activated receptor gamma is inhibited by phosphorylation at a consensus mitogen-activated protein kinase site. *J Biol Chem* 1997; 272: 5128-5132 [PMID: 9005579 DOI: 10.1074/jbc.272.8.5128]

26 **Sahmani M**, Sakhinia E, Farzadi L, Najafipour P, Darabi M, Mehdizadeh A, Shahnazi V, Shaker M, Noori M. Two common polymorphisms in the peroxisome proliferator-activated receptor γ gene may improve fertilization in IVF. *Reprod Biomed Online* 2011; 23: 355-360 [PMID: 21764381 DOI: 10.1016/j.rbmo.2011.05.009]

27 **Cheatham WW**. Peroxisome proliferator-activated receptor translational research and clinical experience. *Am J Clin Nutr* 2010; 91: 2625-2665 [DOI: 10.3945/ajcn.2009.28449D]

28 **Lennon AM**, Ramaugé M, Dessouroux A, Pierre M. MAP kinase cascades are activated in astrocytes and preadipocytes by 15-deoxy-Delta(12,14)-prostaglandin J2 and the thiazolidinedione ciglitazone through peroxisome proliferator activator receptor gamma-independent mechanisms involving re-active oxygenated species. *J Biol Chem* 2002; 277: 29681-29685 [PMID: 12052825 DOI: 10.1074/jbc.M201517200]

29 **Toyama T**, Kudo N, Hibiyo Y, Mitsumoto A, Nishikawa M, Kawashima Y. Effects of pioglitazone on steroyl-CoA desaturation in obese Zucker fa/fa rats. *J Pharmacol Sci* 2007; 104: 137-145 [PMID: 17538229 DOI: 10.1254/jphs.FP060997]

30 **Montanaro MA**, Lombardo YB, González MS, Bernasconi AM, Chicco A, Rimoldi OJ, Basabe JC, Brenner RR. Effect of troglitazone on the desaturases in a rat model of insulin resistance induced by a sucrrose-rich diet. *Prostaglandins Leukot Essent Fatty Acids* 2005; 72: 241-250 [PMID: 15763435 DOI: 10.1016/j.plefa.2004.11.003]

31 **Wahl HG**, Kausch C, Machicao F, Rett K, Stumvoll M, Häring HU. Troglitazone downregulates delta-6 desaturase gene expression in human skeletal muscle cell cultures. *Diabetes* 2002; 51: 1060-1065 [PMID: 11916926 DOI: 10.2337/diabetes.51.4.1060]

32 **Deeban R**, Maerz-Weiss P, Catlett NL, Steiner G, Wong B, Wright MB, Blander G, Elliston KO, Ladd W, Bobadilla M, Mizrahi J, Haefliger C, Edgar A. Comparative transcriptional network modeling of three PPAR-α/γ co-agonists reveals distinct metabolic gene signatures in primary human hepatocytes. *PLoS One* 2012; 7: e55012 [PMID: 22514701 DOI: 10.1371/journal.pone.0055012]

33 **Kahn CR**, Chen L, Cohen SE. Unraveling the mechanism of action of thiazolidinediones. *J Clin Invest* 2000; 106: 1305-1307 [PMID: 11104782 DOI: 10.1172/JCI11705]

34 **Li Y**, Lazar MA. Differential gene regulation by PPARgamma agonist and constitutively active PPARgamma2. *Mol Endocrinol* 2002; 16: 1040-1048 [PMID: 11981038 DOI: 10.1210/me.16.5.1040]

35 **Risérus U**, Tan GD, Fielding BA, Neville MJ, Currie J, Savage DB, Chatterjee VK, Frayn KN, O’Rahilly S, Karpe F. Rosiglitazone increases indexes of steroyl-CoA desaturase activity in humans: link to insulin sensitization and the role of dominant-negative mutation in peroxisome proliferator-activated receptor-gamma. *Diabetes* 2005; 54: 1379-1384 [PMID: 15855323 DOI: 10.2373/diabetes.54.5.1379]

36 **Stefan N**, Peter A, Cegan A, Staiger H, Machann J, Schick F, Clausen CD, Fritsche A, Häring HU, Schleicher E. Low hepatic steroyl-CoA desaturase I activity is associated with fatty liver and insulin resistance in obese humans. *Diabetologia* 2008; 51: 648-656 [PMID: 18286258 DOI: 10.1007/s00125-008-0938-7]

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