

Role of peroxisome proliferator-activated receptors alpha and gamma in gastric ulcer: An overview of experimental evidences

Lekha Saha

Lekha Saha, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

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Correspondence to: Lekha Saha, Associate Professor, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India. lekhasaha@rediffmail.com
Telephone: +91-172-2755253
Fax: +91-172-2744401

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. Three subtypes, PPAR α , PPAR β/δ , and PPAR γ , have been identified

so far. PPAR α is expressed in the liver, kidney, small intestine, heart, and muscle, where it activates the fatty acid catabolism and control lipoprotein assembly in response to long-chain unsaturated fatty acids, eicosanoids, and hypolipidemic drugs (*e.g.*, fenofibrate). PPAR β/δ is more broadly expressed and is implicated in fatty acid oxidation, keratinocyte differentiation, wound healing, and macrophage response to very low density lipoprotein metabolism. This isoform has been implicated in transcriptional-repression functions and has been shown to repress the activity of PPAR α or PPAR γ target genes. PPAR γ 1 and γ 2 are generated from a single-gene peroxisome proliferator-activated receptors gamma by differential promoter usage and alternative splicing. PPAR γ 1 is expressed in colon, immune system (*e.g.*, monocytes and macrophages), and other tissues where it participates in the modulation of inflammation, cell proliferation, and differentiation. PPARs regulate gene expression through distinct mechanisms: Ligand-dependent transactivation, ligand-independent repression, and ligand-dependent transrepression. Studies in animals have demonstrated the gastric antisecretory activity of PPAR α agonists like ciprofibrate, bezafibrate and clofibrate. Study by Pathak *et al* also demonstrated the effect of PPAR α agonist, bezafibrate, on gastric secretion and gastric cytoprotection in various gastric ulcer models in rats. The majority of the experimental studies is on pioglitazone and rosiglitazone, which are PPAR γ activators. In all the studies, both the PPAR γ activators showed protection against the gastric ulcer and also accelerate the ulcer healing in gastric ulcer model in rats. Therefore, PPAR α and PPAR γ may be a target for gastric ulcer therapy. Finally, more studies are also needed to confirm the involvement of PPARs α and γ in gastric ulcer.

Key words: Peroxisome proliferator-activated receptors; Gastric ulcer; Evidences

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Core tip: Peroxisome proliferator-activated receptors (PPARs) are a nuclear hormone receptor family and act as transcription factors. PPARs are of three subtypes, *i.e.*, PPAR α , PPAR β/δ , and PPAR γ . The common sites where PPAR α is expressed are muscle, heart, liver, small intestine and kidney. PPAR γ is involved in modulation of various functions like inflammation, cell proliferation, and differentiation and it is commonly expressed in white blood cells (*e.g.*, macrophages and monocytes) which are involved in immune activity and in the colon. Studies in animals have demonstrated the gastric antisecretory activity of PPAR α agonists like ciprofibrate, bezafibrate and clofibrate. The majority of the experimental studies regarding the role of PPAR γ activators is on pioglitazone and rosiglitazone. In all the studies, both the PPAR γ activators showed protection against the gastric ulcer and also accelerate the ulcer healing in gastric ulcer model in rats. Therefore, PPAR α and PPAR γ can be explored as a target of gastric ulcer treatment. The aim of the present paper is to discuss the experimental evidences of the role of PPARs in gastric ulcer.

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INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are a nuclear hormone receptor family and act as transcription factors. PPARs are of three subtypes, *i.e.*, PPAR α , PPAR β/δ , and PPAR γ . PPAR α is involved in fatty acid catabolism and also in controlling of lipoprotein assembly. Factors which activate PPAR α are hypolipidemic drugs (*e.g.*, Fenofibrate), long-chain unsaturated fatty acids and eicosanoids. PPAR α is distributed in many tissues like heart, kidney, muscle, liver, and small intestine^[1,2]. PPAR β/δ isoform of PPARs has been shown to involve in transcriptional-repression functions and inhibits PPAR α or PPAR γ target genes^[2-7]. This isoform is abundantly distributed in the body and take part in various activities like keratinocyte differentiation, fatty acid oxidation, healing and very low density lipoprotein metabolism. PPAR γ 1 and γ 2 are two subtype of PPAR γ and derived from a single gene peroxisome proliferator-activated receptors gamma^[8-12]. PPAR γ 1 is involved in modulation of various physiological functions like inflammation, cell proliferation, and differentiation and is found in tissues like white blood cells (*e.g.*, monocytes and macrophages) of the immune system, colon, and other tissues. Whereas PPAR γ 2 found in adipose tissue and plays an important role in the differentiation of adipocyte, storage

of lipid, and energy dissipation^[12]. Not only that, PPAR γ is also taking part in the metabolism of glucose and improving the insulin sensitivity. Thiazolidinediones which is a PPAR γ agonist, are commonly used for the treatment of type 2 diabetes as insulin-sensitizing drugs^[2,4,5].

Molecular structure of PPARs

PPARs are consist of following function domains: (A/B) N-terminal region, (C) DBD (DNA-binding domain), (D) flexible hinge region, (E) LBD (ligand binding domain) and (F) C-terminal region^[13,14]. The DBD contains two zinc finger motifs, which bind to specific sequences of DNA known as hormone response elements when the receptor is activated. The LBD has an extensive secondary structure consisting of 13 alpha helices and a beta sheet. Natural and synthetic ligands bind to the LBD, either activating or repressing the receptor. The transcriptional activating function (AF-1) motif is present in the N-terminus and it is not activated by ligands. On the other hand, E/F domain or LBD also contains a transcriptional activating function (AF-2) motif at the C-terminus helix 12, which is activated by ligands^[13]. A large numbers of synthetic and natural ligands like eicosanoids, fatty acids, linoleic acid derivatives, oxidized and nitrated fatty acids, bind to the large binding pocket present on the E/F (LBD) domain. The dimerization of PPARs with the 9-cis retinoic acid receptor (RXR) requires both the D and E/F domains. Then this dimerized PPARs and RXR bound to their respective peroxisome proliferator-activated receptor response elements (PPREs) present on the DNA molecule.

Genes which take part in various body functions like the metabolism of lipid, homeostasis of energy, proliferation, differentiation, and survival of cells has their functional PPREs in their regulatory regions^[1,2,13,15].

The expression of various genes which involved in various physiological functions are regulated by PPARs through three mechanisms: Transactivation (ligand-dependent), repression (ligand-independent) and trans-repression (ligand-dependent)^[16,17] (Figure 1).

The classical mode of action of PPARs is the ligand-dependent transactivation. In this mechanism when a ligand binds to the PPARs, there is folding back of the helix 12 of the LBD which leads to the exposure of the AF-2 motif. The AF-2 motif is crucial for the recruitment of transcriptional coactivators. All these changes help in fitting together of all the transcriptional machinery at PPRE-containing promoters^[16,17]. When there is no ligand, transcription of target genes is inhibited by PPARs by recruitment of co repressor complexes like nuclear receptor corepressor and silencing mediator for retinoid and thyroid receptors (Figure 1). "Transrepression" has recently been discovered as an additional nongenomic, ligand-dependent gene repression mechanism of PPARs which involves protein-protein interactions of NF κ B, AP1, Smads, signal transducers and activators of transcription, and nuclear factor of activated T cells^[17-19]. In both the genomic mechanisms of regulation of various genes by PPARs, *i.e.*, repression and transactivation required the

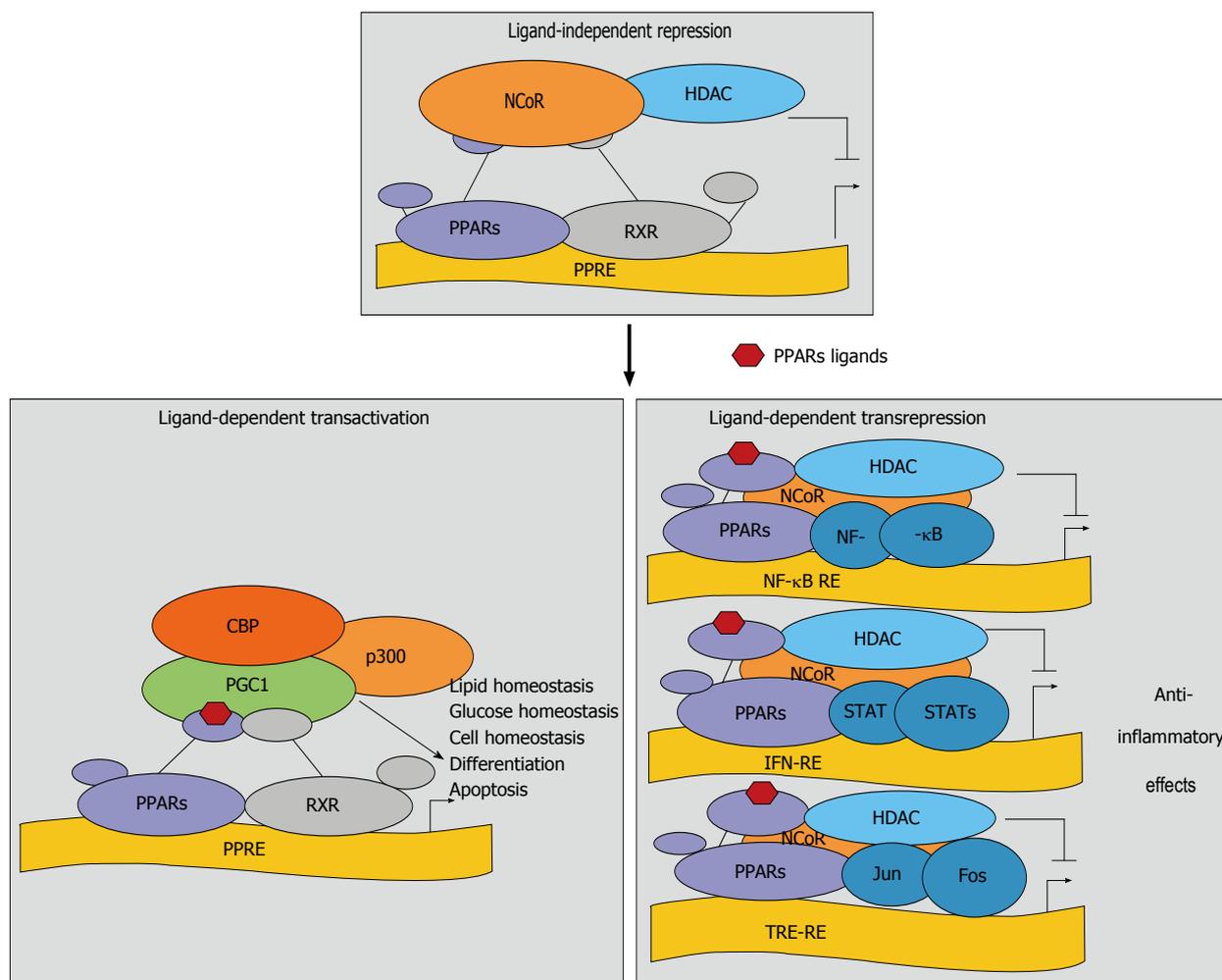


Figure 1 Peroxisome proliferator-activated receptors - mediated mechanisms of transcriptional regulation. In the absence of ligands, peroxisome proliferator-activated receptors (PPARs) bind the promoters of their target genes and repress transcription by recruiting the corepressor complex. In the presence of ligands, PPARs can induce either ligand-dependent transactivation or transrepression. Transactivation involves PPARs heterodimerization with the retinoid X receptors (RXRs) followed by recognition of specific PPAR response elements (PPREs) and interaction with coactivators. Transrepression involves interference with other signal transduction pathways, including NF-κB, STAT, and AP1. NCoR: Nuclear receptor corepressor; NF-κB-RE: NF-κB response element; IFN-RE: Interferon-stimulated gene factor responsive element; TRE-RE: O-tetradecanoylphorbol 13-acetate-responsive element; HDAC: Histone deacetylase; CBP: CREB binding protein; PGC1: Peroxisome proliferator activated receptor gamma coactivator 1; STATs: Signal transducers and activators of transcription.

binding of PPARs to PPREs, but transrepression, which is a nongenomic mechanism, does not require the binding of PPARs to PPREs. The anti-inflammatory properties of PPARs might be explained by the transrepression mechanism, where there is recruitment and stabilization of the corepressor complexes on the promoters of pro-inflammatory genes^[17-20].

PPAR α and gastric ulcer

PPAR α is widely distributed in the small and large intestinal mucosa where dietary fatty acids delivered^[21,22]. The genes which involved in functions like inflammation, cell cycle progression, angiogenesis and lipid metabolism are regulated by PPAR α ^[23-27]. The role of PPAR α in the processes like angiogenesis and cell cycle progression has been suggested its contribution toward the formation and progression tumor. To the best of my knowledge till date, no data have been available which indicates its role in gastric and esophageal cancer. However, its role in

colorectal cancer has been investigated both *in vivo* and *in vitro* studies^[24-30].

PPAR α agonist enhanced the release of gastrin following the stimulation of PPAR α ^[31]. The PPAR α agonist induced hypergastrinemia is associated with less number of granules per cell as well as a relative increase in the number of electron-dense granules. All these changes with PPAR α agonist are similar to those effects induced by proton pump inhibitor, pantoprazole, which indicates the signs of activation of the gastric cells in general^[32]. Gastrin is a peptide hormone. It has two principal biological effects: Stimulation of acid secretion from gastric parietal cells and stimulation of mucosal growth in the acid-secreting part of the stomach (gastric cytoprotective effect)^[33]. Nitric oxide is one of the well know gastro-cytoprotective agent and there is increased in the release of nitric oxide following PPAR α stimulation^[34]. Reports in the published literature have indirectly shown the antigastric ulcer effect of PPAR α .

The gastric antisecretory activity of PPAR α agonists like ciprofibrate, bezafibrate and clofibrate have been demonstrated in animal studies^[35,36]. A short study by Eason *et al*^[36] in the mid-1970s first time demonstrated the antisecretory activity of clofibrate in rats. In the same study other phenoxyisobutyrate derivatives like ciprofibrate and bezafibrate have also demonstrated a significant reduction in gastric acid secretion in rats like clofibrate, but the duration of action of ciprofibrate was longer as compared to ciprofibrate and bezafibrate^[36].

Another study by Pathak *et al*^[35] also studied the effect of bezafibrate, a PPAR α agonist, on acid secretion and gastric cytoprotection in various rat models of gastric ulcer. Various gastric ulcer models were used in this study like acetic acid-induced chronic gastric ulcers, pylorus ligation, ethanol-induced, indomethacin-induced and ischemia-reperfusion-induced gastric ulcers. Bezafibrate (10 mg/kg and 100 mg/kg body weight) were used intraperitoneally. Significant antiulcer effects were seen with both the doses of bezafibrate in all the gastric ulcer models except acetic acid-induced chronic gastric ulcers and ischemia-reperfusion-induced gastric ulcer models. The healing of gastric ulcer was improved with bezafibrate in acetic acid-induced chronic gastric ulcer model. Bezafibrate (10 and 100 mg/kg) was also able to inhibit gastric ulcer formation induced by ischemia-reperfusion. So, this study not only demonstrated the antigastric ulcer property of the PPAR α agonists, but also demonstrated its ulcer healing property in gastric ulcer models in rats^[35].

We have also demonstrated the antigastric ulcer activity of bezafibrate in our laboratory (unpublished data). The present study was undertaken to validate antiulcer activity and the mechanism of action of bezafibrate in gastric ulcer. The aspirin induced gastric ulcer model was used. Bezafibrate was administered in graded doses (10-200 mg/kg) to detect the best effective anti-ulcer dose of bezafibrate. Keeping in view the diversity of defensive mechanisms, the present study was limited to exploring the involvement of the mucosal oxidant system, apoptotic pathway and nitric oxide pathway in the mechanism of the antigastric ulcer effect of bezafibrate. To explore the nitric oxide mechanism, a nitric oxide synthase inhibitor, *N*^o-nitro-L-arginine was used. The following parameters were measured: Ulcer Index, Histopathological scoring of gastric ulcer, gastric juice analysis, Gastric mucosal lipid peroxidation parameters, Estimation of nitric oxide metabolite in blood, mRNA expression of inducible nitric oxide synthase (iNOS) and constitutive nitric oxide synthase (cNOS) enzyme in gastric mucosa, Gastric mucosal DNA fragmentation study. Bezafibrate demonstrated dose-dependent antiulcer activity, showed antisecretory and gastro protective action, reduced lipid peroxidation, inhibit iNOS expression, preserve cNOS expression and qualitatively inhibited DNA fragmentation and improved upon the Histopathological score of gastric mucosa.

The histopathological findings of the gastric mucosa:

Aspirin administration showed superficial erosion and ulceration on the mucosa and infiltration of inflammatory cells. Co administration of bezafibrate with aspirin showed gastric mucosa with reepithilization, formation of pits and decreased infiltration of inflammatory cells. From this finding we can say that bezafibrate (a PPAR α agonist) might have an anti inflammatory activity in gastric ulcer. This is the new finding seen with Bezafibrate and if proven clinically can be used in combination with aspirin (unpublished data).

PPAR γ AND GASTRIC ULCER

PPAR γ is a subtype type of PPARs which is a nuclear hormone receptor super family. The transcription of numerous cellular processes and various cytokines is controlled by activation of PPAR γ ^[37]. The function and differentiation of immune cells and synthesis of many inflammatory cytokines like tumor necrosis factor alpha (TNF- α) might be controlled by stimulation of PPAR γ ^[38]. Cytoprotective and antioxidant activities of PPAR γ activation have been demonstrated in several experimental studies^[39]. The role of PPAR γ has been implicated in various disease conditions like atherosclerosis, inflammation, cancer and infertility. In adipose tissue, PPAR γ is highly expressed and it plays an important role in the differentiation of adipocyte and maintenance of insulin responses.

PPAR γ is widely distributed in the colon and the major sources might be the macrophages and epithelial cells. The other tissues which expressed PPAR γ are small intestine, liver, pancreas and stomach. Low concentrations of PPAR γ are seen in tissues like kidneys, glial cells, cartilage, airway epithelial cells and skin. Whereas gene of PPAR γ is almost undetectable in muscles^[40]. In spite the fact that colonic epithelial cells highly expressed PPAR γ , investigators have also demonstrated the effect of the PPAR γ /RXR in gastric disorders. Most gastric cancer cell lines expressed PPAR γ and RXR α both at mRNA and protein level^[41]. Studies have not been fully explored the distribution of PPAR γ in human stomach tissue. In the published literatures, reports are there about the constitutive and the ubiquitous expression of PPAR γ mainly by epithelial cells in normal human gastric mucosa^[42]. During gastritis, there noticeably increased in the expression of PPAR γ in gastric mucosa^[41]. This finding may substantiate the preventive regulatory role of PPAR γ in inflammatory cascade and could be a target for the prevention of gastric inflammation. This hypothesis has been supported by many studies in which PPAR γ agonists demonstrated the protective role in gastric inflammation in chemical-induced gastritis models in rats^[43,44]. A study by Hamaguchi *et al*^[43] demonstrated the ulcer healing property of 15d-prostaglandin J2, a natural PPAR γ agonist, in gastric ulcer model without the effect on gastric-acid secretion. A study by Takagi *et al*^[44] also supported this finding of Hamaguchi and colleagues by demonstrating the beneficial effects of pioglitazone, a specific ligand of PPAR γ on aspirin-induced

gastric mucosal injury, which could be attributable to the inhibition of production of gastric TNF- α . Another study by Naito *et al*^[45] further substantiated the anti-inflammatory properties of pioglitazone in experimentally induced gastric mucosal injury in rat which could be attributable to its. Naito *et al*^[45] also explores the antioxidative property of pioglitazone in their study. The ulcer healing property of pioglitazone was also demonstrated by Konturek *et al*^[46] in rat. They determined the effect of pioglitazone on the healing of gastric ulcers in rats. Konturek *et al*^[46] explored the following parameters in their study to demonstrate the ulcer healing property of pioglitazone: Measuring the gastric mucosal blood flow, measuring the expression of various cytokines like interleukin-1 α , TNF- α and measuring the expression of various protective proteins like heat shock protein 70 (HSP70), cNOS, iNOS, cyclooxygenase-1 and cyclooxygenase-2 in gastric mucosa. There was significant increased in gastric ulcer healing by pioglitazone pre-treatment as there was significant increased in blood flow at the ulcer margin and there was reduction in the area of gastric ulcers. There was significant increased in the expression of PPAR γ mRNA in the gastric mucosa (ulcerated). Therefore the study by Konturek *et al*^[46] demonstrated the ulcer healing property of pioglitazone and also supports the anti-inflammatory action of pioglitazone.

The gastroprotective effect of another PPAR γ agonist, rosiglitazone, has been documented by Villegas *et al*^[47] against ischemia - reperfusion induced injury in the rat stomach. The potent gastro protective and ulcer healing properties of pioglitazone was also determined in another study by Brzozowski *et al*^[37]. In this study, the authors were also able to demonstrate the role of endogenous PG and NO in gastroprotective and hyperaemic actions of pioglitazone. There were significantly decreased in the release and expression of various proinflammatory cytokines like TNF- α and IL-1 β by pioglitazone. The acceleration of ulcer healing by the PPAR γ ligand may be attributed to the increase in angiogenesis at the ulcer margin by a significant increase in the expression of PECAM-1 protein, a marker of angiogenesis^[37].

The latest study by El-Moselhy *et al*^[48] further documented the involvement of PPAR γ activation in nitric oxide mediated gastric ulcer healing in rats. Stress - induced ulcer model was used in this study. The nitric oxide pathway was explored. To demonstrate the gastroprotective effect of rosiglitazone, the authors used the following groups of animals: Rosiglitazone alone treated group, rosiglitazone + PPAR γ antagonist (BADGE) group, rosiglitazone + nitric oxide synthase inhibitor (L-NAME) group. The authors concluded that the gastroprotective effect of rosiglitazone might be because of its antisecretory, antioxidant and anti-inflammatory properties^[48].

CONCLUSION

The findings of the experimental studies suggest the involvement of PPAR α and γ in gastric ulcer. Regarding the involvement of PPAR α , there are two studies

published in the literature which showed gastric antisecretory effects of phenoxyisobutyrate (ciprofibrate, bezafibrate and clofibrate) and gastric cytoprotective effects of bezafibrate in the rat gastric ulcer model. The majority of the experimental studies is on pioglitazone and rosiglitazone, which are PPAR γ activators. In all the studies, both the PPAR γ activators showed protection against the gastric ulcer and also accelerate the ulcer healing in gastric ulcer model in rats. The mechanisms involved in the protection of gastric ulcer explored in these studies are antioxidant activity, anti-inflammatory activity, angiogenic activity and over expression of HSP70. Therefore, PPAR α and PPAR γ may be a target for gastric ulcer therapy. Finally, more studies are also needed to confirm the involvement of PPAR α and γ in gastric ulcer.

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