[Frontiers in Bioscience 19, 916-935, June 1, 2014]

Cross-talk between heme oxygenase and peroxisome proliferator-activated receptors in the regulation of physiological functions

Joseph Fomusi Ndisang[1]

[1]*Department of Physiology, University of Saskatchewan College of Medicine, 107 Wiggins Road, Saskatoon, SK, Canada S7N 5E5*

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1. ABSTRACT

Peroxisome-proliferator-activated-receptors (PPARs) are transcription factors belonging to the superfamily of nuclear receptors. The isoforms of PPAR include PPAR alpha, PPAR gamma and PPAR delta (also known as PPAR beta). Generally, PPARs potentiate insulin sensitivity, improve glucose/lipid metabolism, suppress inflammation/oxidative stress, attenuate excessive immune responses, regulate cell-growth and differentiation. Interestingly, agonists of PPAR gamma and PPAR alpha have been shown to upregulate the heme-oxygenase (HO)-system. Conversely, the HO-system also enhances PPAR alpha, and potentiates the expression and activity of PPARγ. Moreover, the HO-system and related products including bilirubin, biliverdin, carbon monoxide and ferritin have been shown to increase insulin sensitivity, improve glucose/lipid metabolism, suppress inflammation/oxidative stress, abate immune response, and modulate cell-growth/differentiation. Therefore, an intimate, reciprocal, stimulatory and synergistic relationship between PPAR-signaling and the HO-system can be envisaged in the regulation of physiological functions. Thus, both the HO-system and PPARs-signaling participate in fine-tuning similar physiological functions, so novel pharmacological agents capable of optimizing this interaction should be sought. The coordinated regulation of PPAR-signaling and the HO-system may constitute the basis for future drug design.

2. INTRODUCTION

Transcription factors are biosensors that modulate physiological processes by converting signals generated by cells into gene expression after binding to specific DNA sequence in gene promoters. Interestingly, a specific signaling pathway can activate multiple transcription factors, and conversely, the expression of a specific gene may be controlled by a wide spectrum of different transcription factors.

Peroxisome-proliferator-activated-receptors (PPARs) are transcription factors belonging to the superfamily of nuclear receptors and are activated upon binding to specific ligands which are generally small lipophilic molecules (1-11). The superfamily of nuclear receptors include: (i) steroid hormones like progesterone, estrogen, glucocorticoids and mineralocorticoids, (ii) thyroxine, retinoic acid and vitamin D, and (iii) PPARs agonists (1-11). The three commonly described isoforms or subtypes of PPAR includes PPAR alpha, PPAR gamma and PPAR delta (sometimes referred to as PPAR beta) (1-5, 11). PPARs have different tissue distribution and are important regulators of physiological events (1-5, 12-68).

PPARs are intracellular receptors that upon interaction with agonists or ligands like fatty acids or their derivatives translocate to the nucleus to modulate gene transcription. Within the nucleus, PPARs exist as obligate

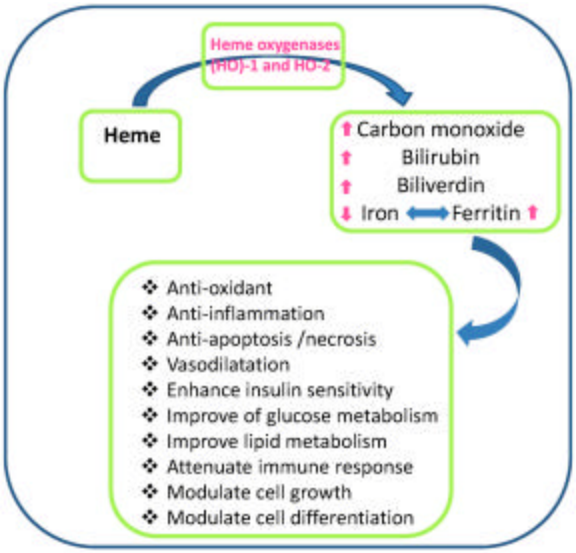

Figure 1. Summary of diverse role of PPARs. The three isoforms of PPAR, namely PPAR alpha, PPAR gamma and PPAR delta (sometimes referred to as PPAR beta) are encoded by distinct genes and are implicated in the regulation of several physiological functions including the potentiation of glucose/lipid metabolism, suppression of inflammatory/oxidative insults, attenuation of immune response, abrogation of apoptosis/necrosis, modulation of vascular tone and the regulation of cell growth and differentiation.

heterodimers with retinoid-X-receptor (RXR) and are anchored to DNA with co-repressor molecules. Upon activation by ligands, the heterodimers undergo conformational changes that cause the dissociation of co-repressors and the recruitment of different transcriptional co-activators and/or co-activator-related proteins, with subsequent modulation of gene transcription, protein synthesis and specific cellular functions (6, 25, 40, 69-75). Generally, PPARs are implicated in a wide range of physiological functions including enhancement of insulin sensitivity, improvement of glucose and lipid metabolism, suppression of inflammatory/oxidative insults, modulation of the immune response and the regulation of cell growth and differentiation (1-5, 11, 29-38).

There is an intimate reciprocal relationship between many transcription factors and the heme oxygenase (HO) system (76-88). The HO system and related products including carbon monoxide, bilirubin, biliverdin and ferritin have gained significant recognition in the regulation of several physiological functions such as insulin sensitivity, glucose metabolism, lipid metabolism, inflammation/oxidative stress, immune response, apoptosis, cell growth and differentiation (89-136). Emerging evidence indicates that many of the effects modulated by the HO system are mediated through different transcription factors, amongst which peroxisome proliferator-activated receptor (PPARs) is of particular interest given its reciprocal, stimulatory and synergistic relationship with the HO system (76-88). HO is a microsomal enzyme that catalyzes the breakdown of the pro-oxidant heme, generating cytoprotective products including biliverdin, bilirubin and carbon monoxide (89, 137-139). The two principal isoforms of HO are HO-1 (inducible) and HO-2 (constitutive), while the third isoform HO-3, is a pseudotranscript of HO-2, so HO activity is largely determined by inputs from HO-1 and HO-2 isoforms (140-142).

Recent studies indicate that HO-1 gene promoter also contains motifs for PPARs response element (82, 84, 85), suggesting that the HO system may regulate PPAR. This notion is further strengthened by reports indicating that the HO system potentiates PPAR alpha (81, 82, 84, 85). On the other hand, the PPAR alpha agonist and lipid-lowering drug, fibrates, have been shown to enhance HO-1 (76). The interaction between the HO system and PPARs may constitute the basis of many beneficial effects against insulin resistant diabetes, hypertension, obesity and related cardiometabolic complications. Thus, the coordinated activity of HO system and PPARs may be important for fine tuning physiological functions and the maintenance of cellular homeostasis.

3. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR)

PPARs are transcription factors belonging to the superfamily of nuclear receptors, and are known to enhance glucose/lipid metabolism, abate inflammatory/oxidative insults, attenuate immune response, suppress apoptosis/necrosis, increase vasodilatation and regulate cell growth and differentiation (Figure 1) (1-11, 29-38, 43-47, 63-68, 143-163).

Like other nuclear receptors, PPARs are activated upon binding to specific ligands or agonists which are generally small lipophilic molecules (1-11) including: (i) steroids like progesterone, estrogen, glucocorticoids and mineralocorticoids, (ii) thyroxine, retinoic acid and vitamin D, and (iii) PPARs agonists (1-11). Upon activation, PPARs undergo conformational changes, and recruit co-activators or release co-repressors, which determines the functional state of the receptor-ligand transcriptional complex and the expression of distinct target genes (1-11). The activities of PPARs are regulated by complex mechanisms involving: (i) ligand-selective and cell-specific interactions with PPAR-binding proteins, (ii) cyclic guanosine monophosphate (cAMP)-response element-binding protein, (iii) different cofactors, (iv) heterodimerization with members of the RXR family, and (v) the activation of kinases and phosphatases to phosphorylate and dephosphorylate a wide variety of substances such as mitogen-activated protein kinases (MAPK), protein kinase A (PKA), protein kinase C (PKC), adenosine monophosphate-activated protein kinase (AMPK), glycogen synthase kinase-3 and other co-factors (6, 25, 40, 69-75).

The three commonly described isoforms of PPAR includes PPAR alpha, PPAR gamma and PPAR delta (sometimes referred to as PPAR beta) (1-6, 11). The

different isoforms are encoded by distinct genes and their distribution pattern in tissues is different (39-47). For example, PPAR alpha is highly expressed in metabolically active tissue like the skeletal muscle, liver, kidneys, heart, brown adipose tissue and intestinal mucosa (39, 41). Similarly, PPAR gamma is widely expressed in tissues like the large intestines, white adipose tissue, spleen and brown adipose tissue (39, 42), although the expression of PPAR gamma is particularly high in adipose tissue (40). On the other hand, the distribution of PPAR delta is more ubiquitous than PPAR alpha, PPAR gamma (43, 44, 46, 47), and has been reported in a variety of tissues and/or cells across different organs and systems including nervous, hematopoietic, reproductive, immune, cardiovascular, urinary, respiratory, digestive, endocrine, musculoskeletal, sensory and the islet of Langerhans systems (43-47). All PPAR isoforms are composed of a C-terminal ligand-binding domain and an N-terminal DNA-binding domain linked to each other by a hinge region for the interaction of specific PPAR response elements in the promoter region of PPAR-regulated target genes (1-6, 11). Given that each PPAR isoform controls the expression of multiple genes, the activation of PPAR alpha, PPAR gamma and PPAR delta by a given upstream signal, whether a synthetic agonist or a natural ligand, would ultimately lead to the modulation of several genes and corresponding proteins. Accordingly, PPARs are implicated in a wide range of physiological functions including enhancement of insulin sensitivity, improvement of glucose and lipid metabolism, suppression of inflammatory/oxidative insults, modulation of the immune response and the regulation of cell growth and differentiation (1-5, 29-38).

Since transcriptional PPAR responses are triggered by ligand-induced recruitment and/or the release of small accessory molecules which may be co-activators and co-repressors, PPARs can positively regulate target genes as observed in the potentiation of insulin signaling and lipid metabolism or repress the transcription of genes as seen during the suppression of inflammation (164-170). Interestingly, the modulation of PPAR activity by cofactors has been explored to design many pharmacological agents like agonists or ligands for PPAR alpha and PPAR gamma (71). In general, PPAR gamma agonists such as thiazolidinediones improve insulin resistance and glucose metabolism, while PPAR alpha agonists such as fibrates improve dyslipidemia (12-25, 171). The concomitant activation of receptors of PPAR alpha and PPAR gamma may yield a synergistic effect of greater physiological relevance in the homeostatic control of hyperglycemia and cardiac dysfunction associated with diabetes. Accordingly, an emerging trend in PPAR research is formulation of pan-PPAR ligands capable of simultaneously activating two or all three PPAR isoforms (7, 24, 25, 71, 172-175), with the hope of identifying more potent pharmacological response. Accordingly, several dual PPAR alpha/gamma agonists including aleglitazar, muraglitazar and tesaglitazar are currently under development at different phases of clinical trials (7, 25, 174, 175). The results of these clinical trials have yielded mixed results because of serious adverse effects such as bladder cancer and hyperplasia observed with ragaglitazar, MK-0767, and naveglitazar (176, 177), posing further challenges for the formulation of agonist with better safety profile. The search for more-specific PPAR gamma and PPAR alpha agonists continues and candidate products such as INT131, MK0533 and ATx008-001/ FK614 for PPAR gamma (18, 178, 179), as well as other candidate compounds like derivatives of bis-oximinoalkanoic acid for PPAR alpha (180) are presently under development. However, many of such agonists are also noted for excessive side effects because the cofactors that modulate PPAR activity also have the intrinsic ability to regulate a wide spectrum of metabolic processes (71, 181, 182). Besides the development of dual PPAR alpha/gamma agonists, ambitious studies have been designed to formulate agonists capable of concomitantly stimulating all three PPAR isoforms (PPAR alpha, PPAR gamma and PPAR delta) (172, 173). Accordingly, the PPAR alpha/gamma/delta agonist, sipoglitazar is at phase II clinical trials for possible use against type-2 diabetes (172, 173). Whether these generations of new agonist would yield the desired pharmacological effects remains the subject of more intense investigations.

Although the therapeutic potential of PPAR agonists remains enormous, many challenges have to be overcome. Besides collateral effects, recent findings indicate that the different PPAR agonists may have opposing effects. For example, pioglitazone a PPAR gamma agonist, has been shown to improve cardiovascular function, while another PPAR gamma agonist, rosiglitazone, reportedly aggravated the risk of myocardial infarction in clinical trials (25). Similarly, pan-PPAR alpha/gamma agonists such as muraglitazar and tesaglitazar have also encountered setbacks in clinics because of excessive adverse effects (25), whereas another pan-PPAR alpha/gamma agonist such as aleglitazar showed promising results in phase-II clinical trials with benefits on glucose and lipid metabolism (25). These conflicting clinical observations from different PPAR gamma agonists constitute an important drawback that needs to be thoroughly investigated. To improve the benefit-to-risk ratio, it is imperative to formulate novel PPAR agonists with greater selectivity, enhanced efficacy, but less collateral effects. The quest for PPAR agonists with such rigorous prerequisites have led to the inception of several novel candidate compounds including the partial PPAR gamma agonists INT131, MK0533 and ATx008-001/ FK614 (18, 178, 179). Although these studies are still preliminary, the initial results are quite promising.

Given that diverse role of PPARs in regulating physiological functions and the existence of different isoforms (PPAR alpha, PPAR gamma and PPAR delta), the formulation of specific agonists and blockers of these isoforms are needed to assess the specific input and relative contribution of each isoform in regulating physiological functions. Whether the different tissue distribution of PPARs in different tissues (39-42) (43-47) would affect the relative effect in specific tissue needs further clarification because tissue-specific responses is a common phenomenon in physiological milieu (183, 184). Nevertheless, the formulation of specific triad PPAR gamma/alpha/delta agonists may be more effective because

the synergism and/or additive effects of the single agonists for PPAR gamma, PPAR alpha, and PPAR delta. Since PPAR gamma agonists like thiazolidinediones improve insulin resistance and glucose metabolism, while PPAR alpha agonists such as fibrates improve dyslipidemia, and emerging evidence indicate that PPAR delta modulates energy balance, weight loss, skeletal muscle endurance, lipid metabolism and insulin sensitivity (12-25, 45, 46, 64-66, 171, 185), the formulation of selective triad PPAR gamma/alpha/delta agonists may confer greater benefits in patients co-morbid with insulin resistant diabetes, dyslipidemia, obesity and related cardiometabolic complications.

To further elucidate the role of the different PPAR in the regulation of physiological functions, each of the different isoforms, PPAR gamma, PPAR alpha, and PPAR delta will be elaborated in turn.

3.1. Peroxisome proliferator-activated receptor gamma (PPAR gamma)

Thiazolidinediones is the most common class of PPAR gamma agonists, with congeneric such as troglitazone, rosiglitazone and pioglitazone (7, 25, 174, 175). Thiazolidinediones are well known for their role in enhancing insulin sensitivity and glucose metabolism by increasing insulin-stimulated glucose uptake in adipose tissue, skeletal muscle cells and hepatocytes, while decreasing hepatic gluconeogenesis (12-28). An interesting pharmacological characteristic of PPAR gamma agonists is their ability to evoke lasting glucose-lowering effect in type-2 diabetic patients without causing hypoglycaemia and gastrointestinal problems that commonly occur with the administration of other anti-diabetic agents like metformin and sulphonylureas (186). In spite of these positive attributes of PPAR gamma agonists, adverse effects associated with PPAR gamma such as bone fractures, macular oedema, heart failure, peripheral oedema and weight gain are amongst the setbacks that must be addressed (187-190). Thus the formulation of alternative PPAR gamma agonists with reduced collateral effects is imperative. A recent development in this line include the formulation of glitazars, an investigational class of dual-PPAR alpha/gamma agonists in phase-III clinical trials and have been shown to improve insulin sensitivity and glucose metabolism (7, 25, 174, 175). However, further research to fully characterize glitazars and more-importantly for the inception of more selective PPAR gamma agonist besides thiazolidinediones is needed.

Besides their ability to improve glucose metabolism, the activation of PPAR gamma is also beneficial in the cardiovascular system (28, 191-193). PPAR gamma agonists improve cardiovascular risk factors such as blood pressure, lipid metabolism, enhance adiponectin and mitigate inflammation peripherally (28, 191-197), as well as inflammation associated with chronic and acute neurological insults (29). Other relevant physiological effects of PPAR gamma include: (i) the suppression of fibrosis, (ii) reduction of deposition of extracellular matrix/profibrotic proteins such as fibronectin, collagen and transforming growth factor-beta in tissues, (iii) the attenuation of apoptosis, (iv) the suppression of necrosis, and (v) the enhancement of vasorelaxation and thus the regulation of blood pressure (34-36, 147-150, 154-158). Thus, PPAR gamma is implicated in a wide range of physiological functions relevant to energy metabolism, tissue defense, the maintenance of intact structural morphology and blood pressure homeostasis. Although PPAR gamma abates hypertrophic growth mediated by extracellular matrix/profibrotic (34-36), emerging evidence indicate that PPAR gamma regulates the differentiation of trophoblasts, adipocytes and mesenchymal cells (48, 49, 198-200). In a related-study, PPAR gamma was shown to play an integral role in sustaining and optimizing trophoblast differentiation (48). In a similar way, cyclin G2, an unconventional cyclin that is generally upregulated during apoptosis or growth inhibition was shown to activate PPAR gamma during adipocyte differentiation (49). These studies suggest that PPAR gamma may be important for tissue turnover by selectively abating hypertrophic growth while promoting tissue regeneration and neogenesis.

The molecular mechanisms underlying the effects of PPAR gamma are not completely elucidated. Although the major effects of PPAR are largely mediated via the regulation of gene expression, emerging evidence indicate that PPAR gamma undergoes posttranslational modifications via SUMOylation to abate inflammation (201-204). Small Ubiquitin like-MOdifier (SUMOylation) is a process of posttranslational modification for the regulation of proteins and cellular functions (201-203). However, further exploration of posttranslational modification by PPAR gamma is needed. Besides its involvement in inflammation novel studies are needed to clarify whether the mechanism of posttranslational modification is more diffused and implicated in other pathophysiological events modulated by PPAR gamma.

3.2. Peroxisome proliferator-activated receptor alpha (PPAR alpha)

PPAR alpha is the target receptor of the lipid-lowering class of drugs known as fibrates and related compounds including fenofibrate, gemfibrozil, benzafibrate, ciprofibrate, and clofibrate which were originally used as an adjunct therapy against hypercholesterolemia (24, 171). PPAR alpha regulates the transcription of many genes involved in lipid metabolism (51), and does so at intracellular and extracellular levels (51). At the intracellular level, PPAR alpha modulate hepatic fatty acid metabolism by enhancing fatty acid oxidation with increased catabolism and reduced synthesis of triglycerides (50, 51). In addition PPAR alpha enhances several important enzymes implicated in lipid metabolism namely: (i) acyl-CoA oxidase, a fundamental enzyme of peroxisomal ß-oxidation; (ii) medium-chain acyl-CoA dehydrogenase, a key factor of mitochondrial ß-oxidation; and (iii) cytochrome P450, a substance implicated in microsomal ?-hydroxylation of fatty acids (51-55). At extracellular level, PPAR alpha modulate lipid metabolism be increasing lipolysis of triglycerides (51, 205), an event that would eventually lead to the formation of HDL like apolipoproteins A-I and A-II (51, 56, 57).

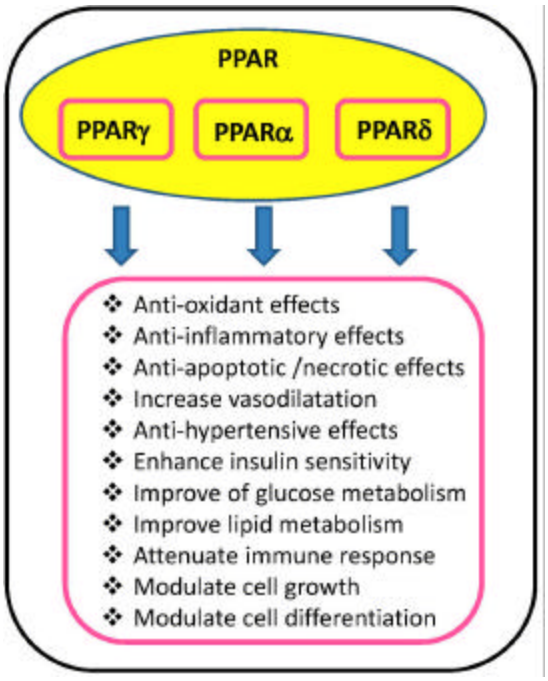

Figure 2. The Heme oxygenase (HO) system and its role in physiological functions. HO catalyzes heme breakdown to yield carbon monoxide, biliverdin, bilirubin and iron, while the iron formed enhances the synthesis of the antioxidant, ferritin. Carbon monoxide, bilirubin, biliverdin and ferritin are implicated in the potentiation of insulin sensitivity, improvement of glucose metabolism, enhancement of lipid metabolism, suppression of inflammation/oxidative stress, attenuation of immune response, reduction of apoptosis and necrosis, and modulation of cell growth and differentiation.

Besides its effects on lipid metabolism, agonists of PPAR alpha are known to suppress inflammation (58-62), modulate the immune response (37, 38), improve glucose metabolism (62, 152, 206), mitigate apoptosis/necrosis and relax vascular tissue (143-153), ameliorate nicotine-induced seizures (207-211) and neuroprotective in Parkinson's disease (212). Similarly, the PPAR alpha agonist, fenofibrate is cardioprotective and has been shown to inhibit left-ventricular hypertrophy, attenuate abnormalities in left-ventricular relaxation and improve systolic dysfunction in Dahl salt-sensitive hypertensive rats (213). Thus, the functions of PPAR alpha agonist not only to optimize lipid and glucose metabolism, but to attenuate inflammatory/immune responses, improve vasodilatation and regulate blood pressure, as well as conferring neuroprotection against seizures and Parkinson's disease. However PPAR alpha agonist have also been shown to induce apoptosis and cancer (214), suggesting the need for more in-depth studies to fully characterize the effects of PPAR alpha agonist in different tissues, especially when administered at different doses.

3.3. Peroxisome proliferator-activated receptor delta (PPAR delta)

PPAR delta (also known as PPAR beta) is widely distributed in tissues and modulate a wide spectrum of physiological functions (43-47, 64-66). These include regulation of cell differentiation, vasodilation, energy balance, weight loss, skeletal muscle endurance and insulin sensitivity (43-47, 63-66, 159-161). Moreover, agonist of PPAR delta such as tesaglitazar, muraglitazar, ragaglitazar, imiglitazar, aleglitazar have been shown to reduce elevated blood glucose levels by altering the body's energy substrate preference from glucose to lipids (24). In addition, PPAR delta suppress inflammation, abates apoptosis, reduce remodeling of vascular tissue and is protective against lipotoxicity (44, 46, 47, 67, 68, 162, 163). These wide spectrum of effects of PPAR delta suggest a in both cellular physiology and pathophysiology effects.

In contrast to agonists of PPAR alpha and PPAR gamma that are used clinically, agonists of PPAR delta are still undergoing development and are at different phases of clinical trials (215-217). Although cytoprotection by PPAR delta (44, 46, 47, 67, 68, 162, 163) and anti-tumorigenic effects of PPAR delta have been reported (218), some reports in literature are not in accordance with this notion. These suggest a proapoptotic role of PPAR delta and its involvement in carcinogenesis (219, 220). These conflicting observations can only be clarified by more intense investigations in this area.

4. THE HEME OXYGENASE (HO) SYSTEM

In the human body, carbon monoxide is produced at a rate of 16.4 micromole per hour and daily production can reach 500 mM (89, 90, 221). About 86% comes from HO-catalyzed degradation of heme while 14% from lipid peroxidation, xenobiotics and other sources (221, 222). HO is a microsomal enzyme that degrades the pro-oxidant heme, generating cytoprotective products including biliverdin, bilirubin and carbon monoxide (Figure 2) (89, 137-139).

Although HO has three isoforms HO-1 (inducible), HO-2 and HO-3 (constitutive), the enzymatic activity is mainly derived from HO-1 and HO-2 because HO-3, has no functional genes in rat and is considered a pseudo-transcript of HO-2 (140-142). In physiological systems, the basal HO activity is maintained by HO-2 (90, 223-226), while HO-1 is activated by physical, chemical and pathophysiological stimuli (90, 226-230).

As such, HO-1 may be considered a sensitive index that is triggered during the onset of pathophysiological changes in cells as an attempt to counteract adverse conditions. However, the pathophysiological activation of HO-1 evokes only a transient or sub-threshold value of HO-activity that is incapable of activating the downstream signaling components of the HO system like the cyclic guanosine monophosphate (cGMP) (90, 99, 100, 231-234), suggesting the need for a robust enhancement of HO-1 by pharmacological agents like hemin, heme arginate, stannous mesoporphyrin, copper protoporphyrin and cobalt protoporphyrin (99, 100, 231-234). Therefore the transient up-regulation of HO-1 that accompanies many pathophysiological conditions may represent the first line of defense mounted by the HO system against tissue insults.

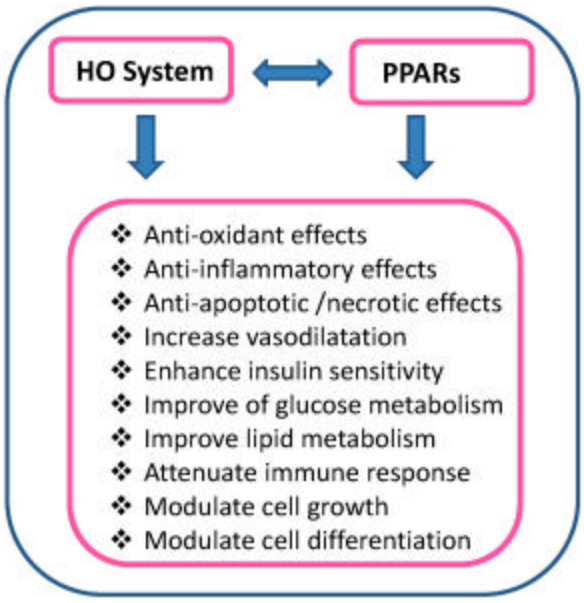

Figure 3. Crosstalk between the HO system and PPARs in regulating physiological functions. There is an intimate reciprocal relationship between PPARs the HO system. Both PPARs and the HO system implicated in a wide range of physiological functions including enhancement of insulin sensitivity, improvement of glucose and lipid metabolism, suppression of inflammatory/oxidative insults, modulation of the immune response and the regulation of cell growth and differentiation.

The HO system and related products such as carbon monoxide, bilirubin, biliverdin and ferritin are of great physiological relevance (89-136). Accordingly, the HO system have been shown to normalize blood pressure in hypertensive animals, enhance insulin sensitivity, improve glucose/lipid metabolism, suppress inflammation/oxidative stress, abate immune response, attenuate apoptosis, and modulate cell growth and differentiation (Figure 2) (89-139, 235-257).

5. CROSSTALK BETWEEN THE HO SYSTEM AND PPARs

Mounting evidence indicates that there is an intimate, reciprocal, stimulatory and synergistic relationship between the HO system and PPARs-signaling (Figure 3) (4, 5, 76-88, 149, 258-274).

Accordingly, PPAR alpha, PPAR gamma and PPAR delta have been shown to upregulate the HO system (4, 5, 76, 78, 82, 84, 149, 268, 270-274). Conversely, the HO system potentiates PPAR alpha and PPAR gamma (81-86, 269, 275). In related studies, PPAR delta and PPAR gamma reportedly induced HO-1 to suppress oxidative stress (4, 78), while PPAR gamma and PPAR delta enhanced HO-1 to attenuate myocardial inflammation and fibrosis with corresponding reduction of myocardial infarction (149, 272). Similarly, PPAR-mediated repression of inflammation and nephrotoxicity was reportedly mitigated via induction of HO-1 (79-81). Furthermore, PPAR delta has been shown to attenuate oxidative stress-induced premature cellular senescence by activating the HO system (271). Interestingly, a product generated by the HO system such as carbon monoxide has also been shown to modulate the expression of PPAR (259, 276). Accordingly, carbon monoxide mitigated inflammation by activating PPAR delta (258). Similarly, carbon monoxide reportedly preserved adequate PPAR gamma levels and suppressed inflammatory insults via PPAR gamma-mediated transcriptional repression of pro-inflammatory genes and proteins (259-265, 276). Furthermore, PPAR gamma and the HO system were shown to evoke vascular relaxation by a common mechanism involving potassium channels (155, 277-280). In related studies PPAR gamma and the HO system triggered vasorelaxation by activating ATP-potassium channels and calcium-activated potassium channels (155, 277-280). Collectively, these studies underscore the multifaceted interaction between the HO system and PPARs in combating tissue insults, potentiating insulin signaling, enhancing lipid/glucose metabolism, modulating vascular tone and relaxation, and thus the maintenance of optimal cellular function and homeostasis.

Although there is compelling evidence supporting the reciprocal, stimulatory and synergistic relationship between the HO system and PPARs-signaling (Figure 3) (4, 5, 76-88, 149, 258-274), further studies are still needed to fully characterize the close interaction between the HO system and PPARs. The interaction may be multifaceted and complex. However, emerging evidence indicates that the HO-1 gene promoter contains motifs for PPAR response element (82, 84, 85). Accordingly, PPAR alpha and PPAR gamma have been shown to transcriptionally induce HO-1 by binding to PPAR responsive elements in HO-1 gene (76, 77). Given that dual-PPAR alpha/gamma agonists (7, 25, 174, 175) and PPAR delta agonist (24) are all known to improve glucose metabolism, and HO-1 gene promoter has motifs for PPAR response element (82, 84, 85), it is possible that the mechanism through the HO system improves glucose/lipid metabolism (89, 91-96, 120, 237, 240, 245, 281) is via the modulation of PPAR agonists. Alternatively, the PPAR response element in HO-1 gene (82, 84, 85) could activate the glucocorticoid-responsive-element in HO-1 gene-promoter (282) to enhance insulin signaling and improve glucose metabolism given that glucocorticoids regulate glucose metabolism and insulin resistance (283). Nevertheless, the interaction between the HO system and PPARs is complex and multifaceted, and the presence of PPAR responsive elements in HO-1 gene (76, 77) may just be one of the facets to a more complex puzzle. Thus, these initial findings may simply represent the tip of the iceberg that should be explored further given the convergence of a wide spectrum physiological functions including the enhancement of insulin sensitivity, improvement of glucose and lipid metabolism, suppression of inflammatory/oxidative insults, attenuation of immune response and the modulation of cell growth and differentiation by PPARs (1-5, 11, 29-38) and the HO system (89-136) (Figure 3).

6. CONCLUSION

The activation of PPARs triggers specific systematic responses through gene regulation. Interestingly,

PPARs can induce or repress the expression of target genes to evoke responses which are channeled to enhance and improve insulin sensitivity, improve glucose/lipid metabolism, but suppress inflammation/oxidative stress, abate the immune response and regulate cell-growth and differentiation (1-5, 29-38). Incidentally, PPAR-signaling is implicated in many effects of the HO system (76-88), and PPAR is potentiated by the HO system (81, 82, 84, 85). Thus, a possible cross-talk between PPARs and the HO system can be envisaged. The existence of an intimate reciprocal relationship between PPAR and the HO system has been further sustained by the presence of motifs of PPAR in HO-1 gene promoter (82, 84, 85). Interestingly, many of the reported physiological effects of PPARs are similar to those evoked by the HO system. Accordingly, the HO system and related products including carbon monoxide, bilirubin, biliverdin and ferritin enhance insulin sensitivity, improve glucose/lipid metabolism, abate apoptosis, inflammation/oxidative stress and immune response and modulate cell growth and differentiation (89-136). Thus, the interaction between the HO system and PPARs may constitute the basis of many beneficial effects against insulin resistant diabetes, hypertension, obesity and related cardiometabolic complications.

Therefore, the coordinated activity between HO system and PPARs is important for fine tuning physiological functions, the maintenance of cellular homeostasis, and more-importantly may constitute the basis for future drug design.

7. ACKNOWLEDGEMENTS

This work was supported by a grant from the Heart & Stroke Foundation of Saskatchewan, Canada to Dr. Joseph Fomusi Ndisang. The author has nothing to disclose. The author has no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

8. REFERENCES

1. T. Lemberger, B. Desvergne and W. Wahli: Peroxisome proliferator-activated receptors: a nuclear receptor signaling pathway in lipid physiology. *Annu Rev Cell Dev Biol*, 12, 335-63 (1996).

2. K. Schoonjans, B. Staels and J. Auwerx: The peroxisome proliferator activated receptors (PPARS) and their effects on lipid metabolism and adipocyte differentiation. *Biochim Biophys Acta*, 1302(2), 93-109 (1996)

3. D. S. Straus and C. K. Glass: Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. *Trends Immunol*, 28(12), 551-8 (2007).

4. F. Ali, N. S. Ali, A. Bauer, J. J. Boyle, S. S. Hamdulay, D. O. Haskard, A. M. Randi and J. C. Mason: PPARdelta and PGC1alpha act cooperatively to induce haem oxygenase-1 and enhance vascular endothelial cell resistance to stress. *Cardiovasc Res*, 85(4), 701-10 (2010).

5. M. Li, Z. Li, X. Sun, L. Yang, P. Fang, Y. Liu, W. Li, J. Xu, J. Lu, M. Xie and D. Zhang: Heme oxygenase-1/p21WAF1 mediates peroxisome proliferator-activated receptor-gamma signaling inhibition of proliferation of rat pulmonary artery smooth muscle cells. *FEBS J*, 277(6), 1543-50 (2010).

6. J. D. Brown and J. Plutzky: Peroxisome proliferator-activated receptors as transcriptional nodal points and therapeutic targets. *Circulation*, 115(4), 518-33 (2007).

7. R. S. Rosenson, R. S. Wright, M. Farkouh and J. Plutzky: Modulating peroxisome proliferator-activated receptors for therapeutic benefit? Biology, clinical experience, and future prospects. *Am Heart J*, 164(5), 672-80 (2012).

8. D. L. Bain, A. F. Heneghan, K. D. Connaghan-Jones and M. T. Miura: Nuclear receptor structure: implications for function. *Annu Rev Physiol*, 69, 201-20 (2007).

9. J. R. Tata: Signalling through nuclear receptors. *Nat Rev Mol Cell Biol*, 3(9), 702-10 (2002).

10. R. C. Ribeiro, P. J. Kushner and J. D. Baxter: The nuclear hormone receptor gene superfamily. *Annu Rev Med*, 46, 443-53 (1995).

11. C. K. Glass and S. Ogawa: Combinatorial roles of nuclear receptors in inflammation and immunity. *Nat Rev Immunol*, 6(1), 44-55 (2006).

12. A. L. Hevener, J. M. Olefsky, D. Reichart, M. T. Nguyen, G. Bandyopadyhay, H. Y. Leung, M. J. Watt, C. Benner, M. A. Febbraio, A. K. Nguyen, B. Folian, S. Subramaniam, F. J. Gonzalez, C. K. Glass and M. Ricote: Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. *J Clin Invest*, 117(6), 1658-69 (2007).

13. H. Kim, M. Haluzik, O. Gavrilova, S. Yakar, J. Portas, H. Sun, U. B. Pajvani, P. E. Scherer and D. LeRoith: Thiazolidinediones improve insulin sensitivity in adipose tissue and reduce the hyperlipidaemia without affecting the hyperglycaemia in a transgenic model of type 2 diabetes. *Diabetologia*, 47(12), 2215-25 (2004).

14. W. Arlt, P. Neogi, C. Gross and W. L. Miller: Cinnamic acid based thiazolidinediones inhibit human P450c17 and 3beta-hydroxysteroid dehydrogenase and improve insulin sensitivity independent of PPARgamma agonist activity. *J Mol Endocrinol*, 32(2), 425-36 (2004)

15. M. Lu, D. A. Sarruf, S. Talukdar, S. Sharma, P. Li, G. Bandyopadhyay, S. Nalbandian, W. Fan, J. R. Gayen, S. K. Mahata, N. J. Webster, M. W. Schwartz and J. M. Olefsky: Brain PPAR-gamma promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. *Nat Med*, 17(5), 618-22 (2011).

16. C. W. Bolten, P. M. Blanner, W. G. McDonald, N. R. Staten, R. A. Mazzarella, G. B. Arhancet, M. F. Meier, D.

J. Weiss, P. M. Sullivan, A. E. Hromockyj, R. F. Kletzien and J. R. Colca: Insulin sensitizing pharmacology of thiazolidinediones correlates with mitochondrial gene expression rather than activation of PPAR gamma. *Gene Regul Syst Bio*, 1, 73-82 (2007)

17. R. Dumasia, K. A. Eagle, E. Kline-Rogers, N. May, L. Cho and D. Mukherjee: Role of PPAR- gamma agonist thiazolidinediones in treatment of pre-diabetic and diabetic individuals: a cardiovascular perspective. *Curr Drug Targets Cardiovasc Haematol Disord*, 5(5), 377-86 (2005)

18. A. Motani, Z. Wang, J. Weiszmann, L. R. McGee, G. Lee, Q. Liu, J. Staunton, Z. Fang, H. Fuentes, M. Lindstrom, J. Liu, D. H. Biermann, J. Jaen, N. P. Walker, R. M. Learned, J. L. Chen and Y. Li: INT131: a selective modulator of PPAR gamma. *J Mol Biol*, 386(5), 1301-11 (2009)

19. J. S. Nam, J. Y. Nam, J. S. Yoo, M. Cho, J. S. Park, C. W. Ahn, B. S. Cha, E. J. Lee, S. K. Lim, K. R. Kim and H. C. Lee: The effect of rosiglitazone on insulin sensitivity and mid-thigh low-density muscle in patients with Type 2 diabetes. *Diabet Med*, 27(1), 30-6 (2010).

20. D. Zhao, B. H. McCully and V. L. Brooks: Rosiglitazone improves insulin sensitivity and baroreflex gain in rats with diet-induced obesity. *J Pharmacol Exp Ther*, 343(1), 206-13 (2012).

21. Y. Miyazaki and R. A. DeFronzo: Rosiglitazone and pioglitazone similarly improve insulin sensitivity and secretion, glucose tolerance and adipocytokines in type 2 diabetic patients. *Diabetes Obes Metab*, 10(12), 1204-11 (2008).

22. Q. Q. Yin, J. J. Pei, S. Xu, D. Z. Luo, S. Q. Dong, M. H. Sun, L. You, Z. J. Sun and X. P. Liu: Pioglitazone improves cognitive function via increasing insulin sensitivity and strengthening antioxidant defense system in fructose-drinking insulin resistance rats. *PLoS One*, 8(3), e59313 (2013).

23. B. Charbonnel, M. Roden, R. Urquhart, S. Mariz, D. Johns, M. Mihm, M. Widel and M. Tan: Pioglitazone elicits long-term improvements in insulin sensitivity in patients with type 2 diabetes: comparisons with gliclazide-based regimens. *Diabetologia*, 48(3), 553-60 (2005).

24. E. Adeghate, A. Adem, M. Y. Hasan, K. Tekes and H. Kalasz: Medicinal Chemistry and Actions of Dual and Pan PPAR Modulators. *Open Med Chem J*, 5(Suppl 2), 93-8 (2011).

25. J. P. Wilding: PPAR agonists for the treatment of cardiovascular disease in patients with diabetes. *Diabetes Obes Metab*, 14(11), 973-82 (2012).

26. M. H. Tan: Current treatment of insulin resistance in type 2 diabetes mellitus. *Int J Clin Pract Suppl*(113), 54-62 (2000)

27. B. M. Spiegelman: PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes*, 47(4), 507-14 (1998)

28. M. A. Deeg and M. H. Tan: Pioglitazone versus Rosiglitazone: Effects on Lipids, Lipoproteins, and Apolipoproteins in Head-to-Head Randomized Clinical Studies. *PPAR Res*, 2008, 520465 (2008).

29. R. Kapadia, J. H. Yi and R. Vemuganti: Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists. *Front Biosci*, 13, 1813-26 (2008)

30. X. R. Chen, V. C. Besson, B. Palmier, Y. Garcia, M. Plotkine and C. Marchand-Leroux: Neurological recovery-promoting, anti-inflammatory, and anti-oxidative effects afforded by fenofibrate, a PPAR alpha agonist, in traumatic brain injury. *J Neurotrauma*, 24(7), 1119-31 (2007).

31. V. Bhatia and P. Viswanathan: Insulin resistance and PPAR insulin sensitizers. *Curr Opin Investig Drugs*, 7(10), 891-7 (2006)

32. X. Yu, X. G. Shao, H. Sun, Y. N. Li, J. Yang, Y. C. Deng and Y. G. Huang: Activation of cerebral peroxisome proliferator-activated receptors gamma exerts neuroprotection by inhibiting oxidative stress following pilocarpine-induced status epilepticus. *Brain Res*, 1200, 146-58 (2008)

33. C. Giaginis, A. Tsantili-Kakoulidou and S. Theocharis: Peroxisome Proliferator-Activated Receptor-gamma Ligands: Potential Pharmacological Agents for Targeting the Angiogenesis Signaling Cascade in Cancer. *PPAR Res*, 2008, 431763 (2008)

34. G. Y. Zhang, T. Cheng, M. H. Zheng, C. G. Yi, H. Pan, Z. J. Li, X. L. Chen, Q. Yu, L. F. Jiang, F. Y. Zhou, X. Y. Li, J. Q. Yang, T. G. Chu and W. Y. Gao: Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist inhibits transforming growth factor-beta1 and matrix production in human dermal fibroblasts. *J Plast Reconstr Aesthet Surg*, 63(7), 1209-16 (2010)

35. G. H. Hao, X. L. Niu, D. F. Gao, J. Wei and N. P. Wang: Agonists at PPAR-gamma suppress angiotensin II-induced production of plasminogen activator inhibitor-1 and extracellular matrix in rat cardiac fibroblasts. *Br J Pharmacol*, 153(7), 1409-19 (2008)

36. D. F. Gao, X. L. Niu, G. H. Hao, N. Peng, J. Wei, N. Ning and N. P. Wang: Rosiglitazone inhibits angiotensin II-induced CTGF expression in vascular smooth muscle cells - role of PPAR-gamma in vascular fibrosis. *Biochem Pharmacol*, 73(2), 185-97 (2007)

37. M. Bionaz, B. J. Thering and J. J. Loor: Fine metabolic regulation in ruminants via nutrient-gene interactions: saturated long-chain fatty acids increase expression of genes involved in lipid metabolism and immune response partly through PPAR-alpha activation. *Br J Nutr*, 107(2), 179-91 (2012)

38. Y. Yang, A. R. Gocke, A. Lovett-Racke, P. D. Drew and M. K. Racke: PPAR Alpha Regulation of the Immune Response and Autoimmune Encephalomyelitis. *PPAR Res*, 2008, 546753 (2008).

39. E. Boitier, J. C. Gautier and R. Roberts: Advances in understanding the regulation of apoptosis and mitosis by peroxisome-proliferator activated receptors in pre-clinical models: relevance for human health and disease. *Comp Hepatol*, 2(1), 3 (2003)

40. P. Tontonoz, E. Hu, R. A. Graves, A. I. Budavari and B. M. Spiegelman: mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev*, 8(10), 1224-34 (1994)

41. F. Beck, S. Plummer, P. V. Senior, S. Byrne, S. Green and W. J. Brammar: The ontogeny of peroxisome-proliferator-activated receptor gene expression in the mouse and rat. *Proc Biol Sci*, 247(1319), 83-7 (1992).

42. A. Mansen, H. Guardiola-Diaz, J. Rafter, C. Branting and J. A. Gustafsson: Expression of the peroxisome proliferator-activated receptor (PPAR) in the mouse colonic mucosa. *Biochem Biophys Res Commun*, 222(3), 844-51 (1996)

43. H. Higashiyama, A. N. Billin, Y. Okamoto, M. Kinoshita and S. Asano: Expression profiling of peroxisome proliferator-activated receptor-delta (PPAR-delta) in mouse tissues using tissue microarray. *Histochem Cell Biol*, 127(5), 485-94 (2007).

44. K. Kang, B. Hatano and C. H. Lee: PPAR delta agonists and metabolic diseases. *Curr Atheroscler Rep*, 9(1), 72-7 (2007)

45. Y. E. Chen, M. Fu, J. Zhang, X. Zhu, Y. Lin, M. A. Akinbami and Q. Song: Peroxisome proliferator-activated receptors and the cardiovascular system. *Vitam Horm*, 66, 157-88 (2003)

46. S. M. Reilly and C. H. Lee: PPAR delta as a therapeutic target in metabolic disease. *FEBS Lett*, 582(1), 26-31 (2008)

47. H. Miyachi: Design, synthesis, and structure-activity relationship study of peroxisome proliferator-activated receptor (PPAR) delta-selective ligands. *Curr Med Chem*, 14(22), 2335-43 (2007)

48. F. P. McCarthy, A. C. Delany, L. C. Kenny and S. K. Walsh: PPAR-gamma -- a possible drug target for complicated pregnancies. *Br J Pharmacol*, 168(5), 1074-85 (2013).

49. V. Aguilar, J. S. Annicotte, X. Escote, J. Vendrell, D. Langin and L. Fajas: Cyclin G2 regulates adipogenesis through PPAR gamma coactivation. *Endocrinology*, 151(11), 5247-54 (2010)

50. G. Martin, K. Schoonjans, A. M. Lefebvre, B. Staels and J. Auwerx: Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. *J Biol Chem*, 272(45), 28210-7 (1997)

51. K. S. Frederiksen, E. M. Wulff, P. Sauerberg, J. P. Mogensen, L. Jeppesen and J. Fleckner: Prediction of PPAR-alpha ligand-mediated physiological changes using gene expression profiles. *J Lipid Res*, 45(3), 592-601 (2004)

52. C. Dreyer, G. Krey, H. Keller, F. Givel, G. Helftenbein and W. Wahli: Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. *Cell*, 68(5), 879-87 (1992)

53. J. D. Tugwood, I. Issemann, R. G. Anderson, K. R. Bundell, W. L. McPheat and S. Green: The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene. *Embo J*, 11(2), 433-9 (1992).

54. T. Gulick, S. Cresci, T. Caira, D. D. Moore and D. P. Kelly: The peroxisome proliferator-activated receptor regulates mitochondrial fatty acid oxidative enzyme gene expression. *Proc Natl Acad Sci U S A*, 91(23), 11012-6 (1994)

55. A. S. Muerhoff, K. J. Griffin and E. F. Johnson: The peroxisome proliferator-activated receptor mediates the induction of CYP4A6, a cytochrome P450 fatty acid omega-hydroxylase, by clofibric acid. *J Biol Chem*, 267(27), 19051-3 (1992)

56. N. Vu-Dac, K. Schoonjans, B. Laine, J. C. Fruchart, J. Auwerx and B. Staels: Negative regulation of the human apolipoprotein A-I promoter by fibrates can be attenuated by the interaction of the peroxisome proliferator-activated receptor with its response element. *J Biol Chem*, 269(49), 31012-8 (1994)

57. N. Vu-Dac, K. Schoonjans, V. Kosykh, J. Dallongeville, J. C. Fruchart, B. Staels and J. Auwerx: Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. *J Clin Invest*, 96(2), 741-50 (1995).

58. S. Dubrac and M. Schmuth: PPAR-alpha in cutaneous inflammation. *Dermatoendocrinol*, 3(1), 23-6 (2011)

59. E. Esposito, E. Mazzon, I. Paterniti, R. Dal Toso, G. Pressi, R. Caminiti and S. Cuzzocrea: PPAR-alpha Contributes to the Anti-Inflammatory Activity of Verbascoside in a Model of Inflammatory Bowel Disease in Mice. *PPAR Res*, 2010, 917312 (2010).

60. E. Rigamonti, G. Chinetti-Gbaguidi and B. Staels: Regulation of macrophage functions by PPAR-alpha, PPAR-gamma, and LXRs in mice and men. *Arterioscler Thromb Vasc Biol*, 28(6), 1050-9 (2008)

61. C. Benito, R. M. Tolon, A. I. Castillo, L. Ruiz-Valdepenas, J. A. Martinez-Orgado, F. J. Fernandez-Sanchez, C. Vazquez, B. F. Cravatt and J. Romero: beta-Amyloid exacerbates inflammation in astrocytes lacking fatty acid amide hydrolase through a mechanism

involving PPAR-alpha, PPAR-gamma and TRPV1, but not CB(1) or CB(2) receptors. *Br J Pharmacol*, 166(4), 1474-89 (2012)

62. V. Lebrun, O. Molendi-Coste, N. Lanthier, C. Sempoux, P. D. Cani, N. van Rooijen, P. Starkel, Y. Horsmans and I. A. Leclercq: Impact of PPAR-alpha induction on glucose homoeostasis in alcohol-fed mice. *Clin Sci (Lond)*, 125(11), 501-11 (2013)

63. A. Lampen, P. A. Grimaldi and H. Nau: Modulation of peroxisome proliferator-activated receptor delta activity affects neural cell adhesion molecule and polysialyltransferase ST8SiaIV induction by teratogenic valproic acid analogs in F9 cell differentiation. *Mol Pharmacol*, 68(1), 193-203 (2005)

64. Y. Oishi, I. Manabe, K. Tobe, M. Ohsugi, T. Kubota, K. Fujiu, K. Maemura, N. Kubota, T. Kadowaki and R. Nagai: SUMOylation of Kruppel-like transcription factor 5 acts as a molecular switch in transcriptional programs of lipid metabolism involving PPAR-delta. *Nat Med*, 14(6), 656-66 (2008)

65. T. Kuroda, H. Hirota, Y. Fujio, S. Sugiyama, M. Masaki, Y. Hiramoto, W. Shioyama, K. Okamoto, M. Hori and K. Yamauchi-Takihara: Carbacyclin induces carnitine palmitoyltransferase-1 in cardiomyocytes via peroxisome proliferator-activated receptor (PPAR) delta independent of the IP receptor signaling pathway. *J Mol Cell Cardiol*, 43(1), 54-62 (2007)

66. G. D. Barish, V. A. Narkar and R. M. Evans: PPAR delta: a dagger in the heart of the metabolic syndrome. *J Clin Invest*, 116(3), 590-7 (2006)

67. I. Paterniti, D. Impellizzeri, R. Crupi, R. Morabito, M. Campolo, E. Esposito and S. Cuzzocrea: Molecular evidence for the involvement of PPAR-delta and PPAR-gamma in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma. *J Neuroinflammation*, 10, 20 (2013)

68. G. Liu, X. Li, Y. Li, X. Tang, J. Xu, R. Li, P. Hao and Y. Sun: PPARdelta agonist GW501516 inhibits PDGF-stimulated pulmonary arterial smooth muscle cell function related to pathological vascular remodeling. *Biomed Res Int*, 2013, 903947 (2013)

69. Y. Kodera, K. Takeyama, A. Murayama, M. Suzawa, Y. Masuhiro and S. Kato: Ligand type-specific interactions of peroxisome proliferator-activated receptor gamma with transcriptional coactivators. *J Biol Chem*, 275(43), 33201-4 (2000)

70. K. A. Burns and J. P. Vanden Heuvel: Modulation of PPAR activity via phosphorylation. *Biochim Biophys Acta*, 1771(8), 952-60 (2007)

71. M. Dietz, P. Mohr, B. Kuhn, H. P. Maerki, P. Hartman, A. Ruf, J. Benz, U. Grether and M. B. Wright: Comparative molecular profiling of the PPARalpha/gamma activator aleglitazar: PPAR selectivity, activity and interaction with cofactors. *ChemMedChem*, 7(6), 1101-11 (2012)

72. J. Mizukami and T. Taniguchi: The antidiabetic agent thiazolidinedione stimulates the interaction between PPAR gamma and CBP. *Biochem Biophys Res Commun*, 240(1), 61-4 (1997)

73. P. Puigserver, Z. Wu, C. W. Park, R. Graves, M. Wright and B. M. Spiegelman: A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell*, 92(6), 829-39 (1998)

74. Y. Jia, G. L. Guo, S. Surapureddi, J. Sarkar, C. Qi, D. Guo, J. Xia, P. Kashireddi, S. Yu, Y. W. Cho, M. S. Rao, B. Kemper, K. Ge, F. J. Gonzalez and J. K. Reddy: Transcription coactivator peroxisome proliferator-activated receptor-binding protein/mediator 1 deficiency abrogates acetaminophen hepatotoxicity. *Proc Natl Acad Sci U S A*, 102(35), 12531-6 (2005)

75. N. Viswakarma, Y. Jia, L. Bai, A. Vluggens, J. Borensztajn, J. Xu and J. K. Reddy: Coactivators in PPAR-Regulated Gene Expression. *PPAR Res*, 2010 (2010)

76. G. Kronke, A. Kadl, E. Ikonomu, S. Bluml, A. Furnkranz, I. J. Sarembock, V. N. Bochkov, M. Exner, B. R. Binder and N. Leitinger: Expression of heme oxygenase-1 in human vascular cells is regulated by peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol*, 27(6), 1276-82 (2007)

77. A. Ptasinska, S. Wang, J. Zhang, R. A. Wesley and R. L. Danner: Nitric oxide activation of peroxisome proliferator-activated receptor gamma through a p38 MAPK signaling pathway. *FASEB J*, 21(3), 950-61 (2007)

78. J. W. Kim, M. H. Li, J. H. Jang, H. K. Na, N. Y. Song, C. Lee, J. A. Johnson and Y. J. Surh: 15-Deoxy-Delta(12,14)-prostaglandin J(2) rescues PC12 cells from H2O2-induced apoptosis through Nrf2-mediated upregulation of heme oxygenase-1: potential roles of Akt and ERK1/2. *Biochem Pharmacol*, 76(11), 1577-89 (2008)

79. P. R. Colville-Nash, S. S. Qureshi, D. Willis and D. A. Willoughby: Inhibition of inducible nitric oxide synthase by peroxisome proliferator-activated receptor agonists: correlation with induction of heme oxygenase 1. *J Immunol*, 161(2), 978-84 (1998)

80. Y. Kitamura, J. Kakimura, Y. Matsuoka, Y. Nomura, P. J. Gebicke-Haerter and T. Taniguchi: Activators of peroxisome proliferator-activated receptor-gamma (PPARgamma) inhibit inducible nitric oxide synthase expression but increase heme oxygenase-1 expression in rat glial cells. *Neurosci Lett*, 262(2), 129-32 (1999)

81. H. H. Chen, T. W. Chen and H. Lin: Pravastatin attenuates carboplatin-induced nephrotoxicity in rodents via peroxisome proliferator-activated receptor alpha-regulated heme oxygenase-1. *Mol Pharmacol*, 78(1), 36-45 (2010)

82. H. Lin, C. H. Yu, C. Y. Jen, C. F. Cheng, Y. Chou, C. C. Chang and S. H. Juan: Adiponectin-mediated heme oxygenase-1 induction protects against iron-induced liver injury via a PPARalpha dependent mechanism. *Am J Pathol*, 177(4), 1697-709 (2010)

83. J. Yu, E. S. Chu, R. Wang, S. Wang, C. W. Wu, V. W. Wong, H. L. Chan, G. C. Farrell and J. J. Sung: Heme oxygenase-1 protects against steatohepatitis in both cultured hepatocytes and mice. *Gastroenterology*, 138(2), 694-704, 704 e1 (2010)

84. C. F. Cheng, W. S. Lian, S. H. Chen, P. F. Lai, H. F. Li, Y. F. Lan, W. T. Cheng and H. Lin: Protective effects of adiponectin against renal ischemia-reperfusion injury via prostacyclin-PPARalpha-heme oxygenase-1 signaling pathway. *J Cell Physiol*, 227(1), 239-49 (2012)

85. H. Lin, W. S. Lian, H. H. Chen, P. F. Lai and C. F. Cheng: Adiponectin ameliorates iron-overload cardiomyopathy through the PPARalpha-PGC-1-dependent signaling pathway. *Mol Pharmacol*, 84(2), 275-85 (2013)

86. M. Bilban, P. Haslinger, J. Prast, F. Klinglmuller, T. Woelfel, S. Haider, A. Sachs, L. E. Otterbein, G. Desoye, U. Hiden, O. Wagner and M. Knofler: Identification of novel trophoblast invasion-related genes: heme oxygenase-1 controls motility via peroxisome proliferator-activated receptor gamma. *Endocrinology*, 150(2), 1000-13 (2009)

87. H. E. Ferguson, T. H. Thatcher, K. C. Olsen, T. M. Garcia-Bates, C. J. Baglole, R. M. Kottmann, E. R. Strong, R. P. Phipps and P. J. Sime: Peroxisome proliferator-activated receptor-gamma ligands induce heme oxygenase-1 in lung fibroblasts by a PPARgamma-independent, glutathione-dependent mechanism. *Am J Physiol Lung Cell Mol Physiol*, 297(5), L912-9 (2009)

88. A. V. Finn, M. John, G. Nakazawa, R. Polavarapu, V. Karmali, X. Xu, Q. Cheng, T. Davis, C. Raghunathan, E. Acampado, T. Ezell, S. Lajoie, M. Eppihimer, F. D. Kolodgie, R. Virmani and H. K. Gold: Differential healing after sirolimus, paclitaxel, and bare metal stent placement in combination with peroxisome proliferator-activator receptor gamma agonists: requirement for mTOR/Akt2 in PPARgamma activation. *Circ Res*, 105(10), 1003-12 (2009)

89. J. F. Ndisang: Role of heme oxygenase in inflammation, insulin-signalling, diabetes and obesity. *Mediators Inflamm*, 2010, 359732 (2010)

90. J. F. Ndisang, H. E. Tabien and R. Wang: Carbon monoxide and hypertension. *J Hypertens*, 22(6), 1057-74 (2004)

91. J. F. Ndisang and A. Jadhav: Heme oxygenase system enhances insulin sensitivity and glucose metabolism in streptozotocin-induced diabetes. *Am J Physiol Endocrinol Metab*, 296(4), E829-41 (2009)

92. J. F. Ndisang and A. Jadhav: Up-regulating the hemeoxygenase system enhances insulin sensitivity and improves glucose metabolism in insulin-resistant diabetes in Goto-Kakizaki rats. *Endocrinology*, 150(6), 2627-36 (2009)

93. J. F. Ndisang, N. Lane and A. Jadhav: The heme oxygenase system abates hyperglycemia in Zucker diabetic fatty rats by potentiating insulin-sensitizing pathways. *Endocrinology*, 150(5), 2098-108 (2009)

94. J. F. Ndisang, N. Lane and A. Jadhav: Upregulation of the heme oxygenase system ameliorates postprandial and fasting hyperglycemia in type 2 diabetes. *Am J Physiol Endocrinol Metab*, 296(5), E1029-41 (2009)

95. J. F. Ndisang, N. Lane, N. Syed and A. Jadhav: Up-regulating the heme oxygenase system with hemin improves insulin sensitivity and glucose metabolism in adult spontaneously hypertensive rats. *Endocrinology*, 151(2), 549-60 (2010)

96. J. F. Ndisang and A. Jadhav: The heme oxygenase system attenuates pancreatic lesions and improves insulin sensitivity and glucose metabolism in deoxycorticosterone acetate hypertension. *Am J Physiol Regul Integr Comp Physiol*, 298(1), R211-23 (2010)

97. A. Jadhav and J. F. Ndisang: Heme arginate suppresses cardiac lesions and hypertrophy in deoxycorticosterone acetate-salt hypertension. *Exp Biol Med (Maywood)*, 234(7), 764-78 (2009)

98. J. F. Ndisang, A. Jadhav and N. Lane: Interaction between the heme oxygenase system and aldosterone in hypertension. *Int J Angiol*, 16(3), 92-97 (2007)

99. J. F. Ndisang, N. Lane and A. Jadhav: Crosstalk between the heme oxygenase system, aldosterone, and phospholipase C in hypertension. *J Hypertens*, 26(6), 1188-99 (2008)

100. J. F. Ndisang and A. Jadhav: Upregulating the heme oxygenase system suppresses left ventricular hypertrophy in adult spontaneously hypertensive rats for 3 months. *J Card Fail*, 15(7), 616-28 (2009)

101. A. Jadhav, E. Torlakovic and J. F. Ndisang: Interaction among heme oxygenase, nuclear factor-kappaB, and transcription activating factors in cardiac hypertrophy in hypertension. *Hypertension*, 52(5), 910-7 (2008)

102. A. Jadhav, E. Torlakovic and J. F. Ndisang: Hemin therapy attenuates kidney injury in deoxycorticosterone acetate-salt hypertensive rats. *Am J Physiol Renal Physiol*, 296(3), F521-34 (2009)

103. M. Zabalgoitia, J. T. Colston, S. V. Reddy, J. W. Holt, R. F. Regan, D. E. Stec, J. M. Rimoldi, A. J. Valente and B. Chandrasekar: Carbon monoxide donors or heme oxygenase-1 (HO-1) overexpression blocks interleukin-18-mediated NF-kappaB-PTEN-dependent human cardiac

endothelial cell death. *Free Radic Biol Med*, 44(3), 284-98 (2008)

104. M. J. Tracz, J. P. Juncos, J. P. Grande, A. J. Croatt, A. W. Ackerman, G. Rajagopalan, K. L. Knutson, A. D. Badley, M. D. Griffin, J. Alam and K. A. Nath: Renal hemodynamic, inflammatory, and apoptotic responses to lipopolysaccharide in HO-1-/- mice. *Am J Pathol*, 170(6), 1820-30 (2007)

105. P. S. Tsai, C. C. Chen, P. S. Tsai, L. C. Yang, W. Y. Huang and C. J. Huang: Heme oxygenase 1, nuclear factor E2-related factor 2, and nuclear factor kappaB are involved in hemin inhibition of type 2 cationic amino acid transporter expression and L-Arginine transport in stimulated macrophages. *Anesthesiology*, 105(6), 1201-10; discussion 5A (2006)

106. M. Chhikara, S. Wang, S. J. Kern, G. A. Ferreyra, J. J. Barb, P. J. Munson and R. L. Danner: Carbon monoxide blocks lipopolysaccharide-induced gene expression by interfering with proximal TLR4 to NF-kappaB signal transduction in human monocytes. *PLoS One*, 4(12), e8139 (2009)

107. J. K. Sarady, S. L. Otterbein, F. Liu, L. E. Otterbein and A. M. Choi: Carbon monoxide modulates endotoxin-induced production of granulocyte macrophage colony-stimulating factor in macrophages. *Am J Respir Cell Mol Biol*, 27(6), 739-45 (2002)

108. R. H. Shih and C. M. Yang: Induction of heme oxygenase-1 attenuates lipopolysaccharide-induced cyclooxygenase-2 expression in mouse brain endothelial cells. *J Neuroinflammation*, 7, 86 (2010)

109. B. Sun, Z. Sun, Q. Jin and X. Chen: CO-releasing molecules (CORM-2)-liberated CO attenuates leukocytes infiltration in the renal tissue of thermally injured mice. *Int J Biol Sci*, 4(3), 176-83 (2008)

110. B. W. Sun, Q. Jin, Y. Sun, Z. W. Sun, X. Chen, Z. Y. Chen and G. Cepinskas: Carbon liberated from CO-releasing molecules attenuates leukocyte infiltration in the small intestine of thermally injured mice. *World J Gastroenterol*, 13(46), 6183-90 (2007)

111. H. Xue, H. Guo, Y. C. Li and Z. M. Hao: Heme oxygenase-1 induction by hemin protects liver cells from ischemia/reperfusion injury in cirrhotic rats. *World J Gastroenterol*, 13(40), 5384-90 (2007)

112. C. D. Jun, Y. Kim, E. Y. Choi, M. Kim, B. Park, B. Youn, K. Yu, K. S. Choi, K. H. Yoon, S. C. Choi, M. S. Lee, K. I. Park, M. Choi, Y. Chung and J. Oh: Gliotoxin reduces the severity of trinitrobenzene sulfonic acid-induced colitis in mice: evidence of the connection between heme oxygenase-1 and the nuclear factor-kappaB pathway *in vitro* and *in vivo*. *Inflamm Bowel Dis*, 12(7), 619-29 (2006)

113. M. P. Seldon, G. Silva, N. Pejanovic, R. Larsen, I. P. Gregoire, J. Filipe, J. Anrather and M. P. Soares: Heme oxygenase-1 inhibits the expression of adhesion molecules associated with endothelial cell activation via inhibition of NF-kappaB RelA phosphorylation at serine 276. *J Immunol*, 179(11), 7840-51 (2007)

114. S. Brouard, P. O. Berberat, E. Tobiasch, M. P. Seldon, F. H. Bach and M. P. Soares: Heme oxygenase-1-derived carbon monoxide requires the activation of transcription factor NF-kappa B to protect endothelial cells from tumor necrosis factor-alpha-mediated apoptosis. *J Biol Chem*, 277(20), 17950-61 (2002)

115. K. Maruyama, E. Morishita, T. Yuno, A. Sekiya, H. Asakura, S. Ohtake and A. Yachie: Carbon monoxide (CO)-releasing molecule-derived CO regulates tissue factor and plasminogen activator inhibitor type 1 in human endothelial cells. *Thromb Res*, 130(3), e188-93 (2012)

116. F. Liu, Z. Y. Du, J. L. He, X. Q. Liu, Q. B. Yu and Y. X. Wang: FTH1 binds to Daxx and inhibits Daxx-mediated cell apoptosis. *Mol Biol Rep*, 39(2), 873-9 (2012)

117. D. Morse, S. E. Pischke, Z. Zhou, R. J. Davis, R. A. Flavell, T. Loop, S. L. Otterbein, L. E. Otterbein and A. M. Choi: Suppression of inflammatory cytokine production by carbon monoxide involves the JNK pathway and AP-1. *J Biol Chem*, 278(39), 36993-8 (2003)

118. L. Conde de la Rosa, T. E. Vrenken, R. A. Hannivoort, M. Buist-Homan, R. Havinga, D. J. Slebos, H. F. Kauffman, K. N. Faber, P. L. Jansen and H. Moshage: Carbon monoxide blocks oxidative stress-induced hepatocyte apoptosis via inhibition of the p54 JNK isoform. *Free Radic Biol Med*, 44(7), 1323-33 (2008)

119. L. M. Tang, Y. P. Wang, K. Wang, L. Y. Pu, F. Zhang, X. C. Li, L. B. Kong, B. C. Sun, G. Q. Li and X. H. Wang: Exogenous biliverdin ameliorates ischemia-reperfusion injury in small-for-size rat liver grafts. *Transplant Proc*, 39(5), 1338-44 (2007)

120. A. Jadhav and J. F. Ndisang: Treatment with heme arginate alleviates adipose tissue inflammation and improves insulin sensitivity and glucose metabolism in a rat model of Human primary aldosteronism. *Free Radic Biol Med*, 53(12), 2277-2286 (2012)

121. A. Jadhav, S. Tiwari, P. Lee and J. F. Ndisang: The heme oxygenase system selectively enhances the anti-inflammatory macrophage-M2 phenotype, reduces pericardial adiposity and ameliorated cardiac injury in diabetic cardiomyopathy in Zucker diabetic fatty rats. *J Pharmacol Exp Ther* (2013)

122. Y. J. Song, Z. M. Zong, H. Z. Liu, R. Mukasa, D. S. Pei, J. Mou, X. R. Wen, Z. A. Liu and X. Y. Wei: Heme oxygenase-1 regulates the JNK signaling pathway through

the MLK3-MKK7-JNK3 signaling module in brain ischemia injury. *Brain Res*, 1429, 1-8 (2012)

123. L. Devey, E. Mohr, C. Bellamy, K. Simpson, N. Henderson, E. M. Harrison, J. A. Ross and S. J. Wigmore: c-Jun terminal kinase-2 gene deleted mice overexpress hemeoxygenase-1 and are protected from hepatic ischemia reperfusion injury. *Transplantation*, 88(3), 308-16 (2009)

124. E. M. George and I. Arany: Induction of heme oxygenase-1 shifts the balance from proinjury to prosurvival in the placentas of pregnant rats with reduced uterine perfusion pressure. *Am J Physiol Regul Integr Comp Physiol*, 302(5), R620-6 (2012)

125. Y. Zheng, Y. Liu, J. Ge, X. Wang, L. Liu, Z. Bu and P. Liu: Resveratrol protects human lens epithelial cells against H2O2-induced oxidative stress by increasing catalase, SOD-1, and HO-1 expression. *Mol Vis*, 16, 1467-74 (2010)

126. E. M. Bulger, I. Garcia and R. V. Maier: Induction of heme-oxygenase 1 inhibits endothelial cell activation by endotoxin and oxidant stress. *Surgery*, 134(2), 146-52 (2003)

127. P. Palozza, S. Serini, D. Curro, G. Calviello, K. Igarashi and C. Mancuso: beta-Carotene and cigarette smoke condensate regulate heme oxygenase-1 and its repressor factor Bach1: relationship with cell growth. *Antioxid Redox Signal*, 8(5-6), 1069-80 (2006)

128. K. J. Peyton, S. V. Reyna, G. B. Chapman, D. Ensenat, X. M. Liu, H. Wang, A. I. Schafer and W. Durante: Heme oxygenase-1-derived carbon monoxide is an autocrine inhibitor of vascular smooth muscle cell growth. *Blood*, 99(12), 4443-8 (2002)

129. K. J. Peyton, A. R. Shebib, M. A. Azam, X. M. Liu, D. A. Tulis and W. Durante: Bilirubin inhibits neointima formation and vascular smooth muscle cell proliferation and migration. *Front Pharmacol*, 3, 48 (2012)

130. N. G. Abraham, T. Kushida, J. McClung, M. Weiss, S. Quan, R. Lafaro, Z. Darzynkiewicz and M. Wolin: Heme oxygenase-1 attenuates glucose-mediated cell growth arrest and apoptosis in human microvessel endothelial cells. *Circ Res*, 93(6), 507-14 (2003)

131. N. W. Cummins, E. A. Weaver, S. M. May, A. J. Croatt, O. Foreman, R. B. Kennedy, G. A. Poland, M. A. Barry, K. A. Nath and A. D. Badley: Heme oxygenase-1 regulates the immune response to influenza virus infection and vaccination in aged mice. *Faseb J*, 26(7), 2911-8 (2012)

132. J. D. Dimitrov, S. Dasgupta, A. M. Navarrete, S. Delignat, Y. Repesse, Y. Meslier, C. Planchais, M. Teyssandier, R. Motterlini, J. Bayry, S. V. Kaveri and S. Lacroix-Desmazes: Induction of heme oxygenase-1 in factor VIII-deficient mice reduces the immune response to therapeutic factor VIII. *Blood*, 115(13), 2682-5 (2010)

133. J. McDaid, K. Yamashita, A. Chora, R. Ollinger, T. B. Strom, X. C. Li, F. H. Bach and M. P. Soares: Heme oxygenase-1 modulates the allo-immune response by promoting activation-induced cell death of T cells. *Faseb J*, 19(3), 458-60 (2005)

134. J. Eiselt, L. Kielberger, T. Sedlackova, J. Racek and P. Pazdiora: High ferritin, but not hepcidin, is associated with a poor immune response to an influenza vaccine in hemodialysis patients. *Nephron Clin Pract*, 115(2), c147-53 (2010)

135. M. Li, G. Saren and S. Zhang: Identification and expression of a ferritin homolog in amphioxus Branchiostoma belcheri: evidence for its dual role in immune response and iron metabolism. *Comp Biochem Physiol B Biochem Mol Biol*, 150(3), 263-70 (2008)

136. R. Ollinger, H. Wang, K. Yamashita, B. Wegiel, M. Thomas, R. Margreiter and F. H. Bach: Therapeutic applications of bilirubin and biliverdin in transplantation. *Antioxid Redox Signal*, 9(12), 2175-85 (2007)

137. M. Mishra and J. F. Ndisang: A critical and comprehensive insight on heme oxygenase and related products including carbon monoxide, bilirubin, biliverdin and ferritin in type-1 and type-2 diabetes. *Curr Pharm Des* (2013)

138. S. Tiwari and J. F. Ndisang: The Heme Oxygenase System and Type-1 Diabetes. *Curr Pharm Des* (2013)

139. S. Tiwari and J. F. Ndisang: Heme Oxygenase System and Hypertension: A Comprehensive Insight. *Curr Pharm Des* (2013)

140. W. K. McCoubrey, Jr., J. F. Ewing and M. D. Maines: Human heme oxygenase-2: characterization and expression of a full-length cDNA and evidence suggesting that the two HO-2 transcripts may differ by choice of polyadenylation signal. *Arch Biochem Biophys*, 295(1), 13-20 (1992)

141. W. K. McCoubrey, Jr., T. J. Huang and M. D. Maines: Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. *Eur J Biochem*, 247(2), 725-32 (1997)

142. S. Hayashi, Y. Omata, H. Sakamoto, Y. Higashimoto, T. Hara, Y. Sagara and M. Noguchi: Characterization of rat heme oxygenase-3 gene. Implication of processed pseudogenes derived from heme oxygenase-2 gene. *Gene*, 336(2), 241-50 (2004)

143. K. Mori, M. Mukoyama and K. Nakao: PPAR-alpha transcriptional activity is required to combat doxorubicin-induced podocyte injury in mice. *Kidney Int*, 79(12), 1274-6 (2011)

144. E. Esposito, B. Rinaldi, E. Mazzon, M. Donniacuo, D. Impellizzeri, I. Paterniti, A. Capuano, P. Bramanti and S. Cuzzocrea: Anti-inflammatory effect of simvastatin in an experimental model of spinal cord trauma: involvement of PPAR-alpha. *J Neuroinflammation*, 9, 81 (2012)

145. M. R. Romano and M. D. Lograno: Involvement of the peroxisome proliferator-activated receptor (PPAR) alpha in vascular response of endocannabinoids in the bovine ophthalmic artery. *Eur J Pharmacol*, 683(1-3), 197-203 (2012)

146. S. E. O'Sullivan: Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol*, 152(5), 576-82 (2007)

147. C. De Ciuceis, F. Amiri, M. Iglarz, J. S. Cohn, R. M. Touyz and E. L. Schiffrin: Synergistic vascular protective effects of combined low doses of PPARalpha and PPARgamma activators in angiotensin II-induced hypertension in rats. *Br J Pharmacol*, 151(1), 45-53 (2007)

148. P. K. Mamnoor, P. Hegde, S. R. Datla, R. K. Damarla, R. Rajagopalan and R. Chakrabarti: Antihypertensive effect of ragaglitazar: a novel PPARalpha and gamma dual activator. *Pharmacol Res*, 54(2), 129-35 (2006)

149. N. S. Wayman, Y. Hattori, M. C. McDonald, H. Mota-Filipe, S. Cuzzocrea, B. Pisano, P. K. Chatterjee and C. Thiemermann: Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size. *FASEB J*, 16(9), 1027-40 (2002)

150. R. A. Roberts, S. Chevalier, S. C. Hasmall, N. H. James, S. C. Cosulich and N. Macdonald: PPAR alpha and the regulation of cell division and apoptosis. *Toxicology*, 181-182, 167-70 (2002)

151. R. A. Roberts, N. H. James, N. J. Woodyatt, N. Macdonald and J. D. Tugwood: Evidence for the suppression of apoptosis by the peroxisome proliferator activated receptor alpha (PPAR alpha)*Carcinogenesis*, 19(1), 43-8 (1998)

152. I. E. Elijah, E. Borsheim, D. M. Maybauer, C. C. Finnerty, D. N. Herndon and M. O. Maybauer: Role of the PPAR-alpha agonist fenofibrate in severe pediatric burn. *Burns*, 38(4), 481-6 (2012)

153. T. C. Jackson, Z. Mi, S. I. Bastacky, T. McHale, M. F. Melhem, P. A. Sonalker, S. P. Tofovic and E. K. Jackson: PPAR alpha agonists improve renal preservation in kidneys subjected to chronic *in vitro* perfusion: interaction with mannitol. *Transpl Int*, 20(3), 277-90 (2007)

154. C. Donovan, X. Tan and J. E. Bourke: PPARgamma Ligands Regulate Noncontractile and Contractile Functions of Airway Smooth Muscle: Implications for Asthma Therapy. *PPAR Res*, 2012, 809164 (2012)

155. H. Kinoshita, T. Azma, H. Iranami, K. Nakahata, Y. Kimoto, M. Dojo, O. Yuge and Y. Hatano: Synthetic peroxisome proliferator-activated receptor-gamma agonists restore impaired vasorelaxation via ATP-sensitive K+ channels by high glucose. *J Pharmacol Exp Ther*, 318(1), 312-8 (2006)

156. H. F. Zhang, L. Wang, H. J. Yuan, Y. H. Ma, Y. F. Wang, Z. Y. Hu, Y. Su and Z. G. Zhao: PPAR-gamma agonist pioglitazone prevents apoptosis of endothelial progenitor cells from rat bone marrow. *Cell Biol Int*, 37(5), 430-5 (2013)

157. H. Kilter, M. Werner, C. Roggia, J. C. Reil, H. J. Schafers, U. Kintscher and M. Bohm: The PPAR-gamma agonist rosiglitazone facilitates Akt rephosphorylation and inhibits apoptosis in cardiomyocytes during hypoxia/reoxygenation. *Diabetes Obes Metab*, 11(11), 1060-7 (2009)

158. B. R. Taira, A. J. Singer, S. A. McClain, F. Lin, J. Rooney, T. Zimmerman and R. A. Clark: Rosiglitazone, a PPAR-gamma ligand, reduces burn progression in rats. *J Burn Care Res*, 30(3), 499-504 (2009)

159. X. Y. Tian, W. T. Wong, N. Wang, Y. Lu, W. S. Cheang, J. Liu, L. Liu, Y. Liu, S. S. Lee, Z. Y. Chen, J. P. Cooke, X. Yao and Y. Huang: PPARdelta activation protects endothelial function in diabetic mice. *Diabetes*, 61(12), 3285-93 (2012)

160. R. Jimenez, M. Sanchez, M. J. Zarzuelo, M. Romero, A. M. Quintela, R. Lopez-Sepulveda, P. Galindo, M. Gomez-Guzman, J. M. Haro, A. Zarzuelo, F. Perez-Vizcaino and J. Duarte: Endothelium-dependent vasodilator effects of peroxisome proliferator-activated receptor beta agonists via the phosphatidyl-inositol-3 kinase-Akt pathway. *J Pharmacol Exp Ther*, 332(2), 554-61 (2010)

161. M. J. Zarzuelo, M. Gomez-Guzman, R. Jimenez, A. M. Quintela, M. Romero, M. Sanchez, A. Zarzuelo, J. Tamargo, F. Perez-Vizcaino and J. Duarte: Effects of peroxisome proliferator-activated receptor-beta activation in endothelin-dependent hypertension. *Cardiovasc Res*, 99(4), 622-31 (2013)

162. Y. Fan, Y. Wang, Z. Tang, H. Zhang, X. Qin, Y. Zhu, Y. Guan, X. Wang, B. Staels, S. Chien and N. Wang: Suppression of pro-inflammatory adhesion molecules by PPAR-delta in human vascular endothelial cells. *Arterioscler Thromb Vasc Biol*, 28(2), 315-21 (2008)

163. R. Di Paola, E. Esposito, E. Mazzon, I. Paterniti, M. Galuppo and S. Cuzzocrea: GW0742, a selective PPAR-beta/delta agonist, contributes to the resolution of inflammation after gut ischemia/reperfusion injury. *J Leukoc Biol*, 88(2), 291-301 (2010)

164. B. H. Lee, W. H. Hsu, Y. Y. Chang, H. F. Kuo, Y. W. Hsu and T. M. Pan: Ankaflavin: a natural novel PPARgamma agonist upregulates Nrf2 to attenuate methylglyoxal-induced diabetes *in vivo. Free Radic Biol Med*, 53(11), 2008-16 (2012)

165. D. Y. Kwon, S. Kim da, H. J. Yang and S. Park: The lignan-rich fractions of Fructus Schisandrae improve insulin sensitivity via the PPAR-gamma pathways in *in vitro* and *in vivo* studies. *J Ethnopharmacol*, 135(2), 455-62 (2011)

166. J. C. de Groot, C. Weidner, J. Krausze, K. Kawamoto, F. C. Schroeder, S. Sauer and K. Bussow: Structural characterization of amorfrutins bound to the peroxisome proliferator-activated receptor gamma. *J Med Chem*, 56(4), 1535-43 (2013)

167. T. Kobayashi and K. Fujimori: Very long-chain-fatty acids enhance adipogenesis through coregulation of Elovl3 and PPARgamma in 3T3-L1 cells. *Am J Physiol Endocrinol Metab*, 302(12), E1461-71 (2012)

168. M. Nie, L. Corbett, A. J. Knox and L. Pang: Differential regulation of chemokine expression by peroxisome proliferator-activated receptor gamma agonists: interactions with glucocorticoids and beta2-agonists. *J Biol Chem*, 280(4), 2550-61 (2005)

169. C. Jiang, A. T. Ting and B. Seed: PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature*, 391(6662), 82-6 (1998)

170. R. B. Tjalkens, X. Liu, B. Mohl, T. Wright, J. A. Moreno, D. L. Carbone and S. Safe: The peroxisome proliferator-activated receptor-gamma agonist 1,1-bis(3'-indolyl)-1-(p-trifluoromethylphenyl)methane suppresses manganese-induced production of nitric oxide in astrocytes and inhibits apoptosis in cocultured PC12 cells. *J Neurosci Res*, 86(3), 618-29 (2008)

171. I. Issemann and S. Green: Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*, 347(6294), 645-50 (1990)

172. F. Stringer, B. A. Ploeger, J. DeJongh, G. Scott, R. Urquhart, A. Karim and M. Danhof: Evaluation of the impact of UGT polymorphism on the pharmacokinetics and pharmacodynamics of the novel PPAR agonist sipoglitazar. *J Clin Pharmacol*, 53(3), 256-63 (2013)

173. F. Stringer, G. Scott, M. Valbuena, J. Kinley, M. Nishihara and R. Urquhart: The effect of genetic polymorphisms in UGT2B15 on the pharmacokinetic profile of sipoglitazar, a novel anti-diabetic agent. *Eur J Clin Pharmacol*, 69(3), 423-30 (2013)

174. B. C. Hansen, X. T. Tigno, A. Benardeau, M. Meyer, E. Sebokova and J. Mizrahi: Effects of aleglitazar, a balanced dual peroxisome proliferator-activated receptor alpha/gamma agonist on glycemic and lipid parameters in a primate model of the metabolic syndrome. *Cardiovasc Diabetol*, 10, 7 (2011)

175. B. Lecka-Czernik: Aleglitazar, a dual PPARalpha and PPARgamma agonist for the potential oral treatment of type 2 diabetes mellitus. *IDrugs*, 13(11), 793-801 (2010)

176. G. G. Long, V. L. Reynolds, A. Lopez-Martinez, T. E. Ryan, S. L. White and S. R. Eldridge: Urothelial carcinogenesis in the urinary bladder of rats treated with naveglitazar, a gamma-dominant PPAR alpha/gamma agonist: lack of evidence for urolithiasis as an inciting event. *Toxicol Pathol*, 36(2), 218-31 (2008)

177. J. P. Wilding, I. Gause-Nilsson and A. Persson: Tesaglitazar, as add-on therapy to sulphonylurea, dose-dependently improves glucose and lipid abnormalities in patients with type 2 diabetes. *Diab Vasc Dis Res*, 4(3), 194-203 (2007)

178. A. M. DePaoli and L. S. Higgins: INT131, a non-TZD selective PPAR gamma modulator (SPPARM), does not cause toxicities typical of TZD full PPAR gamma agonists following 6-month high dose treatment of rats or monkeys. *Diabetologia*, 51, S369-S369 (2008)

179. P. T. Meinke, H. B. Wood and J. W. Szewczyk: Nuclear hormone receptor modulators for the treatment of diabetes and dyslipidemia. In: *Annual Reports in Medicinal Chemistry, Vol 41*. Ed A. Wood. (2006)

180. H. Pingali, M. Jain, S. Shah, P. Zaware, P. Makadia, S. Pola, B. Thube, D. Patel, P. Patil, P. Priyadarshini, D. Suthar, M. Shah, S. Giri and P. Patel: Design and synthesis of novel bis-oximinoalkanoic acids as potent PPAR alpha agonists. *Bioorg Med Chem Lett*, 20(3), 1156-61 (2010)

181. F. Picard and J. Auwerx: PPAR(gamma) and glucose homeostasis. *Annu Rev Nutr*, 22, 167-97 (2002)

182. T. Yamauchi, Y. Oike, J. Kamon, H. Waki, K. Komeda, A. Tsuchida, Y. Date, M. X. Li, H. Miki, Y. Akanuma, R. Nagai, S. Kimura, T. Saheki, M. Nakazato, T. Naitoh, K. Yamamura and T. Kadowaki: Increased insulin sensitivity despite lipodystrophy in Crebbp heterozygous mice. *Nat Genet*, 30(2), 221-6 (2002)

183. A. Farret, R. Filhol, N. Linck, M. Manteghetti, J. Vignon, R. Gross and P. Petit: P2Y receptor mediated modulation of insulin release by a novel generation of 2-substituted-5'-O-(1-boranotriphosphate)-adenosine analogues. *Pharm Res*, 23(11), 2665-71 (2006)

184. X. Zhang, K. S. Lam, H. Ye, S. K. Chung, M. Zhou, Y. Wang and A. Xu: Adipose tissue-specific inhibition of hypoxia-inducible factor 1{alpha} induces obesity and glucose intolerance by impeding energy expenditure in mice. *J Biol Chem*, 285(43), 32869-77 (2010)

185. Y. Kang, X. Huang, E. A. Pasyk, J. Ji, G. G. Holz, M. B. Wheeler, R. G. Tsushima and H. Y. Gaisano: Syntaxin-3 and syntaxin-1A inhibit L-type calcium channel activity, insulin biosynthesis and exocytosis in beta-cell lines. *Diabetologia*, 45(2), 231-41 (2002)

186. C. Sosnowski and E. Janeczko-Sosnowska: [Commentary to the article: Kahn SE, Haffner SM, Heise MA, *et al.* ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355: 2427-43]. *Kardiol Pol*, 65(2), 214-6; discussion 216-7 (2007)

187. Y. Bando, Y. Ushiogi, K. Okafuji, D. Toya, N. Tanaka and M. Fujisawa: Troglitazone combination therapy in obese type 2 diabetic patients poorly controlled with alpha-glucosidase inhibitors. *J Int Med Res*, 27(2), 53-64 (1999)

188. A. Grey: Skeletal consequences of thiazolidinedione therapy. *Osteoporos Int*, 19(2), 129-37 (2008)

189. B. Balas, R. Belfort, S. A. Harrison, C. Darland, J. Finch, S. Schenker, A. Gastaldelli and K. Cusi: Pioglitazone treatment increases whole body fat but not total body water in patients with non-alcoholic steatohepatitis. *J Hepatol*, 47(4), 565-70 (2007)

190. A. Rubenstrunk, R. Hanf, D. W. Hum, J. C. Fruchart and B. Staels: Safety issues and prospects for future generations of PPAR modulators. *Biochim Biophys Acta*, 1771(8), 1065-81 (2007)

191. A. Krishnaswami, S. Ravi-Kumar and J. M. Lewis: Thiazolidinediones: a 2010 perspective. *Perm J*, 14(3), 64-72 (2010)

192. A. Sugawara, A. Uruno, M. Kudo, K. Matsuda, C. W. Yang and S. Ito: Effects of PPARgamma on hypertension, atherosclerosis, and chronic kidney disease. *Endocr J*, 57(10), 847-52 (2010)

193. P. A. Sarafidis and A. N. Lasaridis: Actions of peroxisome proliferator-activated receptors-gamma agonists explaining a possible blood pressure-lowering effect. *Am J Hypertens*, 19(6), 646-53 (2006)

194. A. E. Caballero, R. Saouaf, S. C. Lim, O. Hamdy, K. Abou-Elenin, C. O'Connor, F. W. Logerfo, E. S. Horton and A. Veves: The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. *Metabolism*, 52(2), 173-80 (2003)

195. N. Marx, A. Imhof, J. Froehlich, L. Siam, J. Ittner, G. Wierse, A. Schmidt, W. Maerz, V. Hombach and W. Koenig: Effect of rosiglitazone treatment on soluble CD40L in patients with type 2 diabetes and coronary artery disease. *Circulation*, 107(15), 1954-7 (2003)

196. S. M. Haffner, A. S. Greenberg, W. M. Weston, H. Chen, K. Williams and M. I. Freed: Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation*, 106(6), 679-84 (2002)

197. V. Pasceri, H. D. Wu, J. T. Willerson and E. T. Yeh: Modulation of vascular inflammation *in vitro* and *in vivo* by peroxisome proliferator-activated receptor-gamma activators. *Circulation*, 101(3), 235-8 (2000)

198. I. Takada, A. P. Kouzmenko and S. Kato: PPAR-gamma Signaling Crosstalk in Mesenchymal Stem Cells. *PPAR Res*, 2010 (2010)

199. D. W. Shin, S. N. Kim, S. M. Lee, W. Lee, M. J. Song, S. M. Park, T. R. Lee, J. H. Baik, H. K. Kim, J. H. Hong and M. Noh: (-)-Catechin promotes adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR gamma transactivation. *Biochem Pharmacol*, 77(1), 125-33 (2009)

200. T. Yazawa, Y. Inaoka, R. Okada, T. Mizutani, Y. Yamazaki, Y. Usami, M. Kuribayashi, M. Orisaka, A. Umezawa and K. Miyamoto: PPAR-gamma coactivator-1alpha regulates progesterone production in ovarian granulosa cells with SF-1 and LRH-1. *Mol Endocrinol*, 24(3), 485-96 (2010)

201. G. Pascual, A. L. Fong, S. Ogawa, A. Gamliel, A. C. Li, V. Perissi, D. W. Rose, T. M. Willson, M. G. Rosenfeld and C. K. Glass: A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature*, 437(7059), 759-63 (2005)

202. A. Luciani, V. R. Villella, A. Vasaturo, I. Giardino, V. Raia, M. Pettoello-Mantovani, M. D'Apolito, S. Guido, T. Leal, S. Quaratino and L. Maiuri: SUMOylation of tissue transglutaminase as link between oxidative stress and inflammation. *J Immunol*, 183(4), 2775-84 (2009)

203. T. Ohshima, H. Koga and K. Shimotohno: Transcriptional activity of peroxisome proliferator-activated receptor gamma is modulated by SUMO-1 modification. *J Biol Chem*, 279(28), 29551-7 (2004)

204. C. K. Glass: Potential roles of the peroxisome proliferator-activated receptor-gamma in macrophage biology and atherosclerosis. *J Endocrinol*, 169(3), 461-4 (2001)

205. K. Schoonjans, J. Peinado-Onsurbe, A. M. Lefebvre, R. A. Heyman, M. Briggs, S. Deeb, B. Staels and J. Auwerx: PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *Embo J*, 15(19), 5336-48 (1996)

206. A. A. Bulhak, C. Jung, C. G. Ostenson, J. O. Lundberg, P. O. Sjoquist and J. Pernow: PPAR-alpha activation protects the type 2 diabetic myocardium against ischemia-reperfusion injury: involvement of the PI3-Kinase/Akt and NO pathway. *Am J Physiol Heart Circ Physiol*, 296(3), H719-27 (2009)

207. M. Puligheddu, G. Pillolla, M. Melis, S. Lecca, F. Marrosu, M. G. De Montis, S. Scheggi, G. Carta, E. Murru, S. Aroni, A. L. Muntoni and M. Pistis: PPAR-alpha agonists as novel antiepileptic drugs: preclinical findings. *PLoS One*, 8(5), e64541 (2013)

208. R. Adabi Mohazab, M. Javadi-Paydar, B. Delfan and A. R. Dehpour: Possible involvement of PPAR-gamma receptor and nitric oxide pathway in the anticonvulsant effect of acute pioglitazone on pentylenetetrazole-induced seizures in mice. *Epilepsy Res*, 101(1-2), 28-35 (2012)

209. E. A. Jeong, B. T. Jeon, H. J. Shin, N. Kim, D. H. Lee, H. J. Kim, S. S. Kang, G. J. Cho, W. S. Choi and G. S. Roh: Ketogenic diet-induced peroxisome proliferator-activated receptor-gamma activation decreases neuroinflammation in the mouse hippocampus after kainic acid-induced seizures. *Exp Neurol*, 232(2), 195-202 (2011)

210. D. M. Abdallah: Anticonvulsant potential of the peroxisome proliferator-activated receptor gamma agonist pioglitazone in pentylenetetrazole-induced acute seizures and kindling in mice. *Brain Res*, 1351, 246-53 (2010)

211. R. Bhatti, J. Singh, K. Nepali and M. P. Ishar: Possible involvement of PPAR-gamma in the anticonvulsant effect of Aegle marmelos (L.) Correa. *Neurochem Res*, 38(8), 1624-31 (2013)

212. A. R. Carta and A. Pisanu: Modulating microglia activity with PPAR-gamma agonists: a promising therapy for Parkinson's disease? *Neurotox Res*, 23(2), 112-23 (2013)

213. S. Ichihara, K. Obata, Y. Yamada, K. Nagata, A. Noda, G. Ichihara, A. Yamada, T. Kato, H. Izawa, T. Murohara and M. Yokota: Attenuation of cardiac dysfunction by a PPAR-alpha agonist is associated with down-regulation of redox-regulated transcription factors. *J Mol Cell Cardiol*, 41(2), 318-29 (2006)

214. S. A. Saidi, C. M. Holland, D. S. Charnock-Jones and S. K. Smith: *In vitro* and *in vivo* effects of the PPAR-alpha agonists fenofibrate and retinoic acid in endometrial cancer. *Mol Cancer*, 5, 13 (2006)

215. Y. J. Choi, B. K. Roberts, X. Wang, J. C. Geaney, S. Naim, K. Wojnoonski, D. B. Karpf and R. M. Krauss: Effects of the PPAR-delta agonist MBX-8025 on atherogenic dyslipidemia. *Atherosclerosis*, 220(2), 470-6 (2012)

216. M. Thevis, I. Moller, A. Thomas, S. Beuck, G. Rodchenkov, W. Bornatsch, H. Geyer and W. Schanzer: Characterization of two major urinary metabolites of the PPARdelta-agonist GW1516 and implementation of the drug in routine doping controls. *Anal Bioanal Chem*, 396(7), 2479-91 (2010)

217. X. Feng, Z. Luo, L. Ma, S. Ma, D. Yang, Z. Zhao, Z. Yan, H. He, T. Cao, D. Liu and Z. Zhu: Angiotensin II receptor blocker telmisartan enhances running endurance of skeletal muscle through activation of the PPAR-delta/AMPK pathway. *J Cell Mol Med*, 15(7), 1572-81 (2011)

218. L. Yang, J. Zhou, Q. Ma, C. Wang, K. Chen, W. Meng, Y. Yu, Z. Zhou and X. Sun: Knockdown of PPAR delta gene promotes the growth of colon cancer and reduces the sensitivity to bevacizumab in nude mice model. *PLoS One*, 8(4), e60715 (2013)

219. I. Shureiqi, W. Jiang, X. Zuo, Y. Wu, J. B. Stimmel, L. M. Leesnitzer, J. S. Morris, H. Z. Fan, S. M. Fischer and S. M. Lippman: The 15-lipoxygenase-1 product 13-S-hydroxyoctadecadienoic acid down-regulates PPAR-delta to induce apoptosis in colorectal cancer cells. *Proc Natl Acad Sci U S A*, 100(17), 9968-73 (2003)

220. T. Hatae, M. Wada, C. Yokoyama, M. Shimonishi and T. Tanabe: Prostacyclin-dependent apoptosis mediated by PPAR delta. *J Biol Chem*, 276(49), 46260-7 (2001)

221. C. A. Piantadosi: Biological chemistry of carbon monoxide. *Antioxid Redox Signal*, 4(2), 259-70 (2002)

222. G. S. Marks, H. J. Vreman, B. E. McLaughlin, J. F. Brien and K. Nakatsu: Measurement of endogenous carbon monoxide formation in biological systems. *Antioxid Redox Signal*, 4(2), 271-7 (2002)

223. Y. S. Kim, H. Zhuang, R. C. Koehler and S. Dore: Distinct protective mechanisms of HO-1 and HO-2 against hydroperoxide-induced cytotoxicity. *Free Radic Biol Med*, 38(1), 85-92 (2005)

224. H. Zhuang, Y. S. Kim, K. Namiranian and S. Dore: Prostaglandins of J series control heme oxygenase expression: potential significance in modulating neuroinflammation. *Ann N Y Acad Sci*, 993, 208-16; discussion 287-8 (2003)

225. N. G. Abraham, H. Jiang, M. Balazy and A. I. Goodman: Methods for measurements of heme oxygenase (HO) isoforms-mediated synthesis of carbon monoxide and HO-1 and HO-2 proteins. *Methods Mol Med*, 86, 399-411 (2003)

226. N. G. Abraham and A. Kappas: Pharmacological and clinical aspects of heme oxygenase. *Pharmacol Rev*, 60(1), 79-127 (2008)

227. S. M. Keyse and R. M. Tyrrell: Heme oxygenase is the major 32-kDa stress protein induced in human skin fibroblasts by UVA radiation, hydrogen peroxide, and sodium arsenite. *Proc Natl Acad Sci U S A*, 86(1), 99-103 (1989)

228. Y. Wei, X. M. Liu, K. J. Peyton, H. Wang, F. K. Johnson, R. A. Johnson and W. Durante: Hypochlorous acid-induced heme oxygenase-1 gene expression promotes human endothelial cell survival. *Am J Physiol Cell Physiol*, 297(4), C907-15 (2009)

229. T. Mohri, H. Ogura, T. Koh, K. Fujita, Y. Sumi, K. Yoshiya, A. Matsushima, H. Hosotsubo, Y. Kuwagata, H. Tanaka, T. Shimazu and H. Sugimoto: Enhanced expression of intracellular heme oxygenase-1 in deactivated monocytes from patients with severe systemic inflammatory response syndrome. *J Trauma*, 61(3), 616-23; discussion 623 (2006)

230. J. C. Jonas, Y. Guiot, J. Rahier and J. C. Henquin: Haeme-oxygenase 1 expression in rat pancreatic beta cells is stimulated by supraphysiological glucose concentrations and by cyclic AMP. *Diabetologia*, 46(9), 1234-44 (2003)

231. J. F. Ndisang, L. Wu, W. Zhao and R. Wang: Induction of heme oxygenase-1 and stimulation of cGMP production by hemin in aortic tissues from hypertensive rats. *Blood*, 101(10), 3893-900 (2003)

232. M. E. Ndisang JF, Mannaioni PF, Wang R.: Carbon monoxide and cardiovascular inflammation. In: *Carbon monoxide and cardiovascular functions*. Ed I. R. CPC Press, Boca Raton (2002)

233. J. F. Ndisang and A. Jadhav: The heme oxygenase system attenuates pancreatic lesions and improves insulin sensitivity and glucose metabolism in deoxycorticosterone acetate hypertension. *Am J Physiol Regul Integr Comp Physiol* (2009)

234. J. F. Ndisang and R. Wang: Alterations in heme oxygenase/carbon monoxide system in pulmonary arteries in hypertension. *Exp Biol Med (Maywood)*, 228(5), 557-63 (2003)

235. J. Ndisang and A. Jadhav: Synergistic Effect of Heme Oxygenase and Atrial Natriuretic Peptide Against Endothelin-1 and Renal Histopathological Lesions in Deoxycorticosterone-Acetate Hypertension. *Hypertension*, 54(4), E114-E114 (2009)

236. J. F. Ndisang: Pre-Emptive Hemin Therapy Improves Glucose Metabolism and Suppress Diabetic Nephropathy in the First Generation Offspring of Diabetic Rats by Modulating Histone Residues. *Circulation*, 124(21) (2011)

237. J. F. Ndisang: The Heme Oxygenase System Selectively Modulates Proteins Implicated in Metabolism, Oxidative Stress and Inflammation in Spontaneously Hypertensive Rats. *Curr Pharm Des* (2013)

238. J. F. Ndisang, P. Gai, L. Berni, C. Mirabella, R. Baronti, P. F. Mannaioni and E. Masini: Modulation of the immunological response of guinea pig mast cells by carbon monoxide. *Immunopharmacology*, 43(1), 65-73 (1999)

239. J. F. Ndisang, A. Islam and A. Jadhav: Upregulation of Heme Oxygenase Reduces Perirenal Adiposity, and Suppress Diabetic Nephropathy in Zucker Diabetic Fatty Rats. *Hypertension*, 58(5), E125-E125 (2011)

240. J. F. Ndisang and A. Jadhav: The heme oxygenase system potentiates insulin-signalling and enhance glucose metabolism in Zucker Diabetic Fatty rats. *Faseb Journal*, 23 (2009)

241. J. F. Ndisang and A. Jadhav: Heme arginate therapy enhanced adiponectin and atrial natriuretic peptide, but abated endothelin-1 with attenuation of kidney histopathological lesions in mineralocorticoid-induced hypertension. *J Pharmacol Exp Ther*, 334(1), 87-98 (2010)

242. J. F. Ndisang and A. Jadhav: Heme-arginate suppresses phospholipase C and oxidative stress in the mesenteric arterioles of mineralcorticoid-induced hypertensive rats. *Hypertens Res*, 33(4), 338-47 (2010)

243. J. F. Ndisang and A. Jadhav: Induction of heme oxygenase ablates epicardial and perirenal adiposity, and suppress diabetic cardiopathy and nephropathy in insulin-resistant Zucker diabetic fatty rats. *European Heart Journal*, 32, 40-40 (2011)

244. J. F. Ndisang and A. Jadhav: Hemin therapy suppresses inflammation and retroperitoneal adipocyte hypertrophy to improve glucose metabolism in obese rats co-morbid with insulin resistant type-2 diabetes. *Diabetes Obes Metab*, 15(11), 1029-39 (2013)

245. J. F. Ndisang and M. Mishra: The heme oxygenase system selectively suppresses the proinflammatory macrophage m1 phenotype and potentiates insulin signaling in spontaneously hypertensive rats. *Am J Hypertens*, 26(9), 1123-31 (2013)

246. A. Jadhav, S. Tiwari, P. Lee and J. F. Ndisang: The heme oxygenase system selectively enhances the anti-inflammatory macrophage-m2 phenotype, reduces pericardial adiposity, and ameliorated cardiac injury in diabetic cardiomyopathy in zucker diabetic Fatty rats. *J Pharmacol Exp Ther*, 345(2), 239-49 (2013)

247. A. Jadhav, E. Torlakovic and J. F. Ndisang: Interaction Among Heme Oxygenase, Nuclear Factor-{kappa}B, and Transcription Activating Factors in Cardiac Hypertrophy in Hypertension. *Hypertension*, 52, 910-917 (2008)

248. A. Jadhav, E. Torlakovic and J. F. Ndisang: Hemin therapy attenuates kidney injury in deoxycorticosterone acetate-salt hypertensive rats. *Am J Physiol Renal Physiol*, 296(3), F521-F534 (2009)

249. A. Kallin, L. E. Johannessen, P. D. Cani, C. Y. Marbehant, A. Essaghir, F. Foufelle, P. Ferre, C. H. Heldin, N. M. Delzenne and J. B. Demoulin: SREBP-1 regulates the expression of heme oxygenase 1 and the phosphatidylinositol-3 kinase regulatory subunit p55 gamma. *J Lipid Res*, 48(7), 1628-36 (2007)

250. D. Liu, Z. He, L. Wu and Y. Fang: Effects of induction/inhibition of endogenous heme oxygenase-1 on lipid metabolism, endothelial function, and atherosclerosis in rabbits on a high fat diet. *J Pharmacol Sci*, 118(1), 14-24 (2012)

251. L. Vanella, G. Li Volti, S. Guccione, G. Rappazzo, E. Salvo, M. Pappalardo, S. Forte, M. L. Schwartzman and N. G. Abraham: Heme oxygenase-2/adiponectin protein-protein interaction in metabolic syndrome. *Biochem Biophys Res Commun*, 432(4), 606-11 (2013)

252. J. Y. Huang, M. T. Chiang, S. F. Yet and L. Y. Chau: Myeloid heme oxygenase-1 haploinsufficiency reduces high fat diet-induced insulin resistance by affecting adipose macrophage infiltration in mice. *PLoS One*, 7(6), e38626 (2012)

253. A. Belhaj, L. Dewachter, F. Kerbaul, S. Brimioulle, C. Dewachter, R. Naeije and B. Rondelet: Heme oxygenase-1 and inflammation in experimental right ventricular failure

on prolonged overcirculation-induced pulmonary hypertension. *PLoS One*, 8(7), e69470 (2013)

254. K. Kang, C. Nan, D. Fei, X. Meng, W. Liu, W. Zhang, L. Jiang, M. Zhao and S. Pan: Heme oxygenase 1 modulates thrombomodulin and endothelial protein C receptor levels to attenuate septic kidney injury. *Shock*, 40(2), 136-43 (2013)

255. S. Schulz, R. J. Wong, K. Y. Jang, F. Kalish, K. M. Chisholm, H. Zhao, H. J. Vreman, K. G. Sylvester and D. K. Stevenson: Heme oxygenase-1 deficiency promotes the development of necrotizing enterocolitis-like intestinal injury in a newborn mouse model. *Am J Physiol Gastrointest Liver Physiol*, 304(11), G991-G1001 (2013)

256. Y. Zhao, L. Zhang, Y. Qiao, X. Zhou, G. Wu, L. Wang, Y. Peng, X. Dong, H. Huang, L. Si, X. Zhang, J. Li, W. Wang, L. Zhou and X. Gao: Heme Oxygenase-1 Prevents Cardiac Dysfunction in Streptozotocin-Diabetic Mice by Reducing Inflammation, Oxidative Stress, Apoptosis and Enhancing Autophagy. *PLoS One*, 8(9), e75927 (2013)

257. N. Chiang, M. Shinohara, J. Dalli, V. Mirakaj, M. Kibi, A. M. Choi and C. N. Serhan: Inhaled carbon monoxide accelerates resolution of inflammation via unique proresolving mediator-heme oxygenase-1 circuits. *J Immunol*, 190(12), 6378-88 (2013)

258. C. H. Woo, M. P. Massett, T. Shishido, S. Itoh, B. Ding, C. McClain, W. Che, S. R. Vulapalli, C. Yan and J. Abe: ERK5 activation inhibits inflammatory responses via peroxisome proliferator-activated receptor delta (PPARdelta) stimulation. *J Biol Chem*, 281(43), 32164-74 (2006)

259. A. Hoetzel, T. Dolinay, S. Vallbracht, Y. Zhang, H. P. Kim, E. Ifedigbo, S. Alber, A. M. Kaynar, R. Schmidt, S. W. Ryter and A. M. Choi: Carbon monoxide protects against ventilator-induced lung injury via PPAR-gamma and inhibition of Egr-1. *Am J Respir Crit Care Med*, 177(11), 1223-32 (2008)

260. K. Tsoyi, Y. M. Ha, Y. M. Kim, Y. S. Lee, H. J. Kim, H. J. Kim, H. G. Seo, J. H. Lee and K. C. Chang: Activation of PPAR-gamma by carbon monoxide from CORM-2 leads to the inhibition of iNOS but not COX-2 expression in LPS-stimulated macrophages. *Inflammation*, 32(6), 364-71 (2009)

261. M. Bilban, F. H. Bach, S. L. Otterbein, E. Ifedigbo, J. C. d'Avila, H. Esterbauer, B. Y. Chin, A. Usheva, S. C. Robson, O. Wagner and L. E. Otterbein: Carbon monoxide orchestrates a protective response through PPARgamma. *Immunity*, 24(5), 601-10 (2006)

262. R. B. Clark: The role of PPARs in inflammation and immunity. *J Leukoc Biol*, 71(3), 388-400 (2002)

263. I. T. Nizamutdinova, Y. M. Kim, H. J. Kim, H. G. Seo, J. H. Lee and K. C. Chang: Carbon monoxide (from CORM-2) inhibits high glucose-induced ICAM-1 expression via AMP-activated protein kinase and PPAR-gamma activations in endothelial cells. *Atherosclerosis*, 207(2), 405-11 (2009)

264. H. Wang, H. Wu, F. Rocuts, Z. Gu, F. H. Bach and L. E. Otterbein: Activation of peroxisome proliferator-activated receptor gamma prolongs isl*et al*lograft survival. *Cell Transplant*, 21(10), 2111-8 (2012)

265. A. Haschemi, B. Y. Chin, M. Jeitler, H. Esterbauer, O. Wagner, M. Bilban and L. E. Otterbein: Carbon monoxide induced PPARgamma SUMOylation and UCP2 block inflammatory gene expression in macrophages. *PLoS One*, 6(10), e26376 (2011)

266. S. Y. Park, J. U. Bae, K. W. Hong and C. D. Kim: HO-1 Induced by Cilostazol Protects Against TNF-alpha-associated Cytotoxicity via a PPAR-gamma-dependent Pathway in Human Endothelial Cells. *Korean J Physiol Pharmacol*, 15(2), 83-8 (2011)

267. A. von Knethen, H. Neb, V. Morbitzer, M. V. Schmidt, A. M. Kuhn, L. Kuchler and B. Brune: PPARgamma stabilizes HO-1 mRNA in monocytes/macrophages which affects IFN-beta expression. *Free Radic Biol Med*, 51(2), 396-405 (2011)

268. K. Sodhi, N. Puri, D. H. Kim, T. D. Hinds, L. A. Stechschulte, G. Favero, L. Rodella, J. I. Shapiro, D. Jude and N. G. Abraham: PPARdelta binding to heme oxygenase 1 promoter prevents angiotensin II-induced adipocyte dysfunction in Goldblatt hypertensive rats. *Int J Obes (Lond)* (2013)

269. A. Burgess, M. Li, L. Vanella, D. H. Kim, R. Rezzani, L. Rodella, K. Sodhi, M. Canestraro, P. Martasek, S. J. Peterson, A. Kappas and N. G. Abraham: Adipocyte heme oxygenase-1 induction attenuates metabolic syndrome in both male and female obese mice. *Hypertension*, 56(6), 1124-30 (2010)

270. Y. M. Nan, F. Han, L. B. Kong, S. X. Zhao, R. Q. Wang, W. J. Wu and J. Yu: Adenovirus-mediated peroxisome proliferator activated receptor gamma overexpression prevents nutritional fibrotic steatohepatitis in mice. *Scand J Gastroenterol*, 46(3), 358-69 (2011)

271. H. J. Kim, S. A. Ham, K. S. Paek, J. S. Hwang, S. Y. Jung, M. Y. Kim, H. Jin, E. S. Kang, I. S. Woo, H. J. Kim, J. H. Lee, K. C. Chang, C. W. Han and H. G. Seo: Transcriptional up-regulation of antioxidant genes by PPARdelta inhibits angiotensin II-induced premature senescence in vascular smooth muscle cells. *Biochem Biophys Res Commun*, 406(4), 564-9 (2011)

272. A. Sakamoto, M. Hongo, K. Furuta, K. Saito, R. Nagai and N. Ishizaka: Pioglitazone ameliorates systolic and diastolic cardiac dysfunction in rat model of angiotensin II-induced hypertension. *Int J Cardiol* (2012)

273. H. M. El-Gowelli, K. S. Abd-Elrahman, E. I. Saad, S. M. El-Gowilly, A. G. Abdel-Galil and M. M. El-Mas: PPARgamma dependence of cyclosporine-isoprenaline renovascular interaction: roles of nitric oxide synthase and heme oxygenase. *J Cardiovasc Pharmacol*, 58(2), 173-80 (2011)

274. D. H. Kim, J. Liu, S. Bhat, G. Benedict, B. Lecka-Czernik, S. J. Peterson, N. A. Ebraheim and B. E. Heck: Peroxisome proliferator-activated receptor delta agonist attenuates nicotine suppression effect on human mesenchymal stem cell-derived osteogenesis and involves increased expression of heme oxygenase-1. *J Bone Miner Metab*, 31(1), 44-52 (2013)

275. H. Yang, L. F. Zhao, Z. F. Zhao, Y. Wang, J. J. Zhao and L. Zhang: Heme oxygenase-1 prevents liver fibrosis in rats by regulating the expression of PPARgamma and NF-kappaB. *World J Gastroenterol*, 18(14), 1680-8 (2012)

276. J. W. Suliburk, J. L. Ward, K. S. Helmer, S. D. Adams, B. S. Zuckerbraun and D. W. Mercer: Ketamine-induced hepatoprotection: the role of heme oxygenase-1. *Am J Physiol Gastrointest Liver Physiol*, 296(6), G1360-9 (2009)

277. V. Werkstrom, L. Ny, K. Persson and K. E. Andersson: Carbon monoxide-induced relaxation and distribution of haem oxygenase isoenzymes in the pig urethra and lower oesophagogastric junction. *Br J Pharmacol*, 120(2), 312-8 (1997)

278. F. S. Gaskin, K. Kamada, M. Yusof, W. Durante, G. Gross and R. J. Korthuis: AICAR preconditioning prevents postischemic leukocyte rolling and adhesion: role of K(ATP) channels and heme oxygenase. *Microcirculation*, 16(2), 167-76 (2009)

279. M. Bolognesi, D. Sacerdoti, A. Piva, M. Di Pascoli, F. Zampieri, S. Quarta, R. Motterlini, P. Angeli, C. Merkel and A. Gatta: Carbon monoxide-mediated activation of large-conductance calcium-activated potassium channels contributes to mesenteric vasodilatation in cirrhotic rats. *J Pharmacol Exp Ther*, 321(1), 187-94 (2007)

280. D. Sacerdoti, M. Bolognesi, M. Di Pascoli, A. Gatta, J. C. McGiff, M. L. Schwartzman and N. G. Abraham: Rat mesenteric arterial dilator response to 11,12-epoxyeicosatrienoic acid is mediated by activating heme oxygenase. *Am J Physiol Heart Circ Physiol*, 291(4), H1999-2002 (2006)

281. M. Li, D. H. Kim, P. L. Tsenovoy, S. J. Peterson, R. Rezzani, L. F. Rodella, W. S. Aronow, S. Ikehara and N. G. Abraham: Treatment of obese diabetic mice with a heme oxygenase inducer reduces visceral and subcutaneous adiposity, increases adiponectin levels, and improves insulin sensitivity and glucose tolerance. *Diabetes*, 57(6), 1526-35 (2008)

282. Y. Lavrovsky, M. L. Schwartzman, R. D. Levere, A. Kappas and N. G. Abraham: Identification of binding sites for transcription factors NF-kappa B and AP-2 in the promoter region of the human heme oxygenase 1 gene. *Proc Natl Acad Sci U S A*, 91(13), 5987-91 (1994)

283. Y. Liu, Y. Nakagawa, Y. Wang, L. Liu, H. Du, W. Wang, X. Ren, K. Lutfy and T. C. Friedman: Reduction of hepatic glucocorticoid receptor and hexose-6-phosphate dehydrogenase expression ameliorates diet-induced obesity and insulin resistance in mice. *J Mol Endocrinol*, 41(2), 53-64 (2008)

Key Words: Heme oxygenase, Diabetes, Peroxisome proliferator-activated receptor, Oxidative stress, Inflammation, Review

Send correspondence to: Joseph Fomusi Ndisang, Department of Physiology, University of Saskatchewan College of Medicine, 107 Wiggins Road, Saskatoon, SK, Canada S7N 5E5, Tel: 306-966-6533, Fax: 306-966-4298, E-mail: joseph.ndisang@usask.ca