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Novel Therapeutic Agents in Pediatric Sepsis: Peroxisome Proliferator Receptor γ (PPAR γ) Agonists

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Abstract: Sepsis is characterized by a systemic inflammatory response. Systemic physiologic changes can occur and lead to cellular damage and organ failure. The nuclear receptor, peroxisome proliferator-activated receptor-γ (PPARγ), is involved in the regulation of the inflammatory response and is altered in sepsis. Thiazolidinediones (TZDs), and the cyclopentenone prostaglandin, 15d-PGJ_2, are specific PPARγ agonists. Preclinical experimental *in vitro* and *in vivo* studies have demonstrated that pharmacological activation of PPARγ provides potent anti-inflammatory effects. These agents may have effects at altering the inflammatory response in clinical sepsis.

Keywords: PPAR gamma, sepsis, inflammation.

INTRODUCTION

Sepsis is a systemic response to infection and can involve a massive systemic inflammatory response that can lead to multiple organ dysfunction and death. It is a continuum of clinical entities and includes the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. There are well established definitions for the sepsis continuum established for both adult and pediatric patients [1, 2]. Although antibiotic therapy treats the underlying infection, it does not reverse the cascade of signaling events activating the innate immune system. A major pathophysiologic event is that, upon interaction with invading microorganisms, the immuno-competent or parenchymal cells of the host produce an overwhelming amount of endogenous pro-inflammatory mediators. This production is regulated at the nuclear level by a rapid activation of transcription factors.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARs)

PPARs are a large superfamily of nuclear receptors which are ligand-dependent transcription factors that influence cellular responses by altering gene expression. Although PPARs were initially described as important in triglyceride and cholesterol homeostasis these receptors are also important in regulating the inflammatory response [3]. PPARs are found in numerous tissues and immune cells such as lymphocytes, monocytes, macrophages, dendritic cells and granulocytes [4-8]. Three isoforms of the PPAR subfamily have been identified: PPARα, PPARβ or δ, and PPARγ [3, 9].

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PPARγ is important in regulating adipocyte proliferation, glucose homeostasis, and inflammation. Upon ligand binding, PPARγ forms a heterodimer with the retinoic acid receptor (RXR). The interaction with the RXR allows the recruitment of a set of cofactors. This complex binds to the PPAR response element (PPRE) in the promoter region of certain target genes to modulate transcription [10-12]. PPARγ can transactivate and transrepress target genes through ligand-dependent and independent mechanisms [13-16].

MODULATION OF PPARγ ACTIVITY

Inflammatory conditions affect PPARγ expression and function in many tissues including lung, liver, and adipose tissue [17-19]. PPARγ expression was downregulated on the endothelium of thoracic aortas and in the lung in polymicrobial sepsis in rats [18, 19]. Zhou *et al*. demonstrated that hepatic PPARγ protein expression was downregulated in the late stages of polymicrobial sepsis but was maintained early in sepsis [20, 21].

PPARγ activity is also altered in human inflammatory conditions. For example, biopsies obtained from the colon of children with Crohn's disease demonstrated a significant reduction of PPARγ mRNA expression compared to control subjects [22]. Culver *et al*. demonstrated that nuclear PPARγ expression is decreased in alveolar macrophages in patients with the inflammatory disease sarcoidosis [23]. Similarly, patients with multiple sclerosis have a significant reduction in PPARγ protein expression in peripheral blood mononuclear cells (PBMC) [24].

One of the few studies to evaluate PPARγ from patients with sepsis demonstrated an increase in PPARγ expression in T lymphocytes and suggested that PPARγ contributes to T cell apoptosis during sepsis, leading to sepsis-induced lymphopenia [25]. Similar findings on PPARγ were demonstrated by Reddy *et al* in polymorphonuclear (PMN) cells from patients with sepsis. It was found that PPARγ

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mRNA expression was significantly increased in PMNs from patients with sepsis compared to the control group. The authors suggest that PPARγ may play a role in the chemotactic response of PMNs in sepsis [26]. Data from our laboratory demonstrate that PBMCs isolated from children with sepsis demonstrate a decrease in nuclear PPARγ protein expression [27]. However despite this decrease, we found that PPARγ activity was increased in patients with septic shock compared to control patients. The PPARγ activity increase in patients with septic shock may be a result of an increase in plasma levels of the endogenous ligand 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2). Together these studies suggest that PPARγ expression and activity is altered in many inflammatory conditions and in many tissues and immunologic cells.

Changes in PPARγ function may also be reflected in alterations in PPARγ target proteins, such as the plasma adipokines, adiponectin and resistin, which have a PPARγ response element in their promoter regions [28-30]. In a recent clinical study, we have observed that plasma levels of resistin and high molecular weight adiponectin (HMWA), the form of adiponectin with metabolic properties, were increased in children with septic shock on the first day of hospitalization compared with control subjects [27]. Similar to PPARγ activity levels, HMWA and resistin levels were higher in patients with higher PRISM scores. Furthermore, day one resistin levels were higher in patients who did not survive from septic shock compared to survivors from septic shock. These findings suggest that the adipokines, HMWA and resistin, may be used clinically to reflect changes in PPARγ activity and may represent valid biomarkers to predict outcome in patients with sepsis.

The molecular mechanisms, which alter PPARγ in sepsis remain unknown. Post-translational modifications, including phosphorylation, can regulate the function of PPARγ [31]. The AF-1 domain of PPARγ contains a consensus mitogen-activated protein kinase (MAPK) site and phosphorylation at serine residue 82 (or 112 for PPARγ2) leads to inhibition of PPARγ transactivation [32, 33]. Furthermore, this phosphorylated-induced repression is due to conformational changes that lead to altered affinity for ligands and cofactors [32, 33]. Another potential mechanism affecting PPARγ involves changes in co-activator and/or co-repressor activity. Cardiac and adipose PGC-1α expression is decreased after lipopolysaccharide (LPS) administration and this correlates with a decrease in PPARγ target gene activation [34, 35]. The transcription factor FoxO1 can also directly transrepresses PPARγ through direct protein-protein interactions to inhibit PPARγ gene expression [36, 37]. The mechanisms responsible for the changes in PPARγ in sepsis are unknown and are the focus of current investigations.

THE PPARγ LIGANDS AND INFLAMMATION

The insulin-sensitizing drugs, thiazolidinediones (TZDs), and the cyclopentenone prostaglandin, 15d-PGJ_2, are specific PPARγ agonists [11, 12, 38]. Thiazolidinediones are Food and Drug Administration (FDA) approved insulin-sensitizing drugs for the treatment of type 2 diabetes mellitus. However, preclinical experimental *in vitro* and *in vivo* studies have demonstrated that pharmacological activation of PPARγ provides potent anti-inflammatory effects, which may be independent from their metabolic properties. In 1998, Ricote *et al*. and Jiang *et al*. independently made the initial observation that PPARγ is involved in the regulation of the inflammatory response in monocytes/macrophages and raised the possibility that synthetic PPARγ ligands may be of therapeutic value in inflammatory diseases [5, 39]. TZDs include rosiglitazone, pioglitazone, troglitazone, and ciglitazone [40, 41]. There is recent controversy regarding long-term treatment of type II diabetic patients with rosiglitazone and an associated increase in cardiovascular events [42]. Thiazolidinediones remain effective at reducing inflammatory mediators in non-diabetic patients with carotid artery stenosis, metabolic syndrome, and polycystic ovary syndrome [43-45].

The endogenous ligand, 15d-PGJ_2, is produced from arachidonic acid via cyclo-oxygenases (COX). COX-1 is constitutively expressed but COX-2 is induced after LPS stimulation through activation of nuclear factor-κB (NF-κB) [46, 47]. 15d-PGJ_2 can also repress the expression of inflammatory genes in activated macrophages including tumor necrosis factor-α (TNFα) and COX-2 [5]. Data from our laboratory and others demonstrate that, although 15d-PGJ_2 is a PPARγ ligand, its anti-inflammatory effects on NF-κB activation occurs through PPARγ-dependent and independent mechanisms [48-51]. One mechanism by which 15d-PGJ_2 has effects is through binding of the electrophilic carbon in the cyclopentenone ring to cellular proteins, modifying signaling pathways [52]. This mechanism may account for the direct repression of NF-κB by 15d-PGJ_2 [53]. Non-steroidal anti-inflammatory drugs, which inhibit cyclo-oxygenase (COX)-1 and COX-2, such as ibuprofen, indomethacin, flufenamic acid and fenoprofen, also bind to PPARγ and activate PPARγ-dependent transcription, but at much higher concentrations compared to other PPARγ ligands [54].

Clinically, 15d-PGJ_2 production may predict PPARγ activation *in vivo*. 15d-PGJ_2 can be measured in urine, synovial fluid and plasma [55, 56]. Urinary 15d-PGJ_2 has been detected in healthy volunteers in the range of 6 to 7 pg/mg creatinine [55]. Our experimental animal data demonstrates that plasma levels of 15d-PGJ_2 are decreased in sepsis and correlate with a similar decrease in PPARγ activity [57]. In humans, 15d-PGJ_2 levels also correlate with PPARγ activity. Children with resolved sepsis had elevated 15d-PGJ_2 levels compared to patients with the systemic inflammatory response syndrome (SIRS) and septic shock [27]. It is not surprising that 15d-PGJ_2 is activated during the inflammatory response from sepsis. 15d-PGJ_2 is produced from arachidonic acid via cyclo-oxygenases (COX), enzymes known to be induced after LPS stimulation [46]. Therefore, 15d-PGJ_2 levels may be increased in sepsis as a compensatory mechanism and contribute to an increase in PPARγ activity.

PPARγ LIGANDS AND SEPSIS

Several studies have demonstrated that activation of PPARγ by specific ligands significantly improves survival in clinically relevant models of septic shock [18, 19, 58]. The beneficial effect of PPARγ activation is likely to be secondary to inhibition of the production of several inflammatory mediators. Data from our laboratory

demonstrate that treatment with 15d-PGJ_2 and ciglitazone improves hypotension and vascular injury and reduces neutrophil infiltration in the lung, colon and liver following polymicrobial sepsis [18]. Furthermore, this reduction in inflammation leads to significantly improved survival. PPARγ ligands provide beneficial effects through modulating the NF-κB and AP-1 signal transduction pathways. Additionally in a model of endotoxic shock post-treatment with 15d-PGJ_2 improved survival and reduced adhesion molecule expression and neutrophil infiltration through a reduction in NF-κB activation [19].

These potent anti-inflammatory actions of PPARγ ligands have been also demonstrated during the cellular innate immune response to bacterial stimuli. For example, 15d-PGJ_2 and the thiazolidinedione troglitazone suppressed thromboxane 2 (TxB_2) and NO production in a dose dependent manner in rat peritoneal macrophages stimulated with heat-killed *Staphylococcus aureus* or *Escherichia coli* [59]. Ciglitazone-treated C57Bl/6 mice inoculated with *Streptococcus pneumoniae* had fewer bacteria, reduced pro-inflammatory cytokine expression in the lung, and increased survival compared with vehicle-treated mice [60]. This effect however was not secondary to an increase in alveolar macrophage phagocytosis of bacteria.

Other PPARγ activators have been described. Recently, the yellow in phyto-chemical pigment of curry, curcurmin has been demonstrated to exhibit anti-inflammatory properties in a rat model of sepsis by up-regulation of PPARγ expression [21]. Experimental *in vitro* studies in kidney proximal tubular cells have also shown that c-peptide, the 31 amino acid peptide of pro-insulin, induces a concentration-dependent transcriptional activation of PPARγ [61]. Interestingly, when administered *in vivo* to mice subjected to endotoxic shock, c-peptide demonstrated beneficial effects in improving survival and reducing the systemic inflammatory response. This therapeutic effect was associated with activation of PPARγ [62].

CONCLUSION

The PPARγ pathway is clearly altered in inflammatory conditions including sepsis. Experimental *in vitro* and *in vivo* studies demonstrate the benefits of using PPARγ agonists on decreasing the inflammatory response in sepsis. These agents improve outcomes in animal studies. The effects of sepsis on the PPARγ pathway in clinical sepsis demonstrate that the changes in PPARγ changes may be dependent on cell type studied. Furthermore it has not yet been determined whether PPARγ agonists will have an impact clinically in patients with sepsis.

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ABBREVIATIONS

(PPARs) = Peroxisome Proliferator-Activated Receptors

(RXR) = Retinoic acid receptor

(PPRE) = PPAR response element

(PBMC) = Peripheral blood mononuclear cells

(PMN) = Polymorphonuclear

(15d-PGJ_2) = 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2

(HMWA) = High molecular weight adiponectin

(MAPK) = Mitogen-activated protein kinase

(LPS) = Lipopolysaccharide

(TZDs) = Thiazolidinediones

(FDA) = Food and Drug Administration

(COX) = Cyclo-oxygenases

(NF-κB) = Nuclear factor-κB

(TNFα) = Tumor necrosis factor-α

(SIRS) = Systemic inflammatory response syndrome

(TxB_2) = Thromboxane 2

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