Differential effects of dexamethasone and rosiglitazone in a sephadex-induced model of lung inflammation in rats: Possible role of tissue inhibitor of metalloproteinase-3

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ABSTRACT

Objectives: To study the effects of two different classes of drugs in sephadex-induced lung inflammation using rats and explore the potential mechanism(s).

Materials and Methods: Effects of dexamethasone (0.3 mg/kg, p.o.) and rosiglitazone (10 mg/kg, p.o.) treatments were evaluated up to 3 days in sephadex challenged rats. 72 h postsephadex administration, broncho-alveolar lavage fluid (BALF) was collected for cell count and cytokine estimation. Lung tissues were harvested for gene expression and histopathology.

Results: Dexamethasone treatment resulted in significant inhibition of lymphocytes, monocytes, eosinophils and neutrophils, whereas rosiglitazone inhibited eosinophils and neutrophils only. Further, dexamethasone reduced the elevated levels of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) after sephadex challenge while rosiglitazone significantly reduced the PGE2 levels without altering LTB4 in the BALF. Hydroxyproline content in rat lung homogenate was significantly reduced with dexamethasone treatment but not with rosiglitazone. Both the drugs were found to suppress matrix metallo proteinase 9, whereas only dexamethasone showed inhibition of tumor necrosis factor-alpha and up-regulation of tissue inhibitor of metalloproteinase 3 (TIMP-3) expression and preserved the broncho-alveolar microstructure.

Conclusions: Our results revealed that up-regulation of TIMP-3 corroborated well with dexamethasone mediated inhibition of collagen degradation and restoration of alveolar micro-architecture.

KEY WORDS: Dexamethasone, lung inflammation, matrix metalloproteinase 9, rosiglitazone, tissue inhibitor of metalloproteinase 3

Introduction

The sephadex-induced lung inflammation in rat is a model of acute alveolitis and bronchiolitis leading to inflammatory cell infiltration and interstitial edema, which appears parallel to many of the pathophysiological features associated with human interstitial lung diseases.[1] Animal studies of sephadex-induced model clearly represent the patterns of inflammatory characteristics of asthma.[2] Matrix metalloproteinases (MMPs) are one of the major players in airway remodeling process. The MMPs are endopeptidases, which play an important role in physiologic and pathological processes including extracellular matrix (ECM) turnover, tissue degradation and repair, cell migration, and inflammation. Two the secreted MMPs, gelatinase-A (MMP-2) and gelatinase-B (MMP-9) can degrade type-IV collagen, the major collagen in all basement membranes and act on cleaved collagen better than other MMPs.[3] MMP-2 and MMP-9 are the major proteinases involved in bronchial remodeling in asthma.[4] An imbalance in the MMPs and their biologic regulators, like tissue inhibitors of metalloproteinase (TIMPs) may result in matrix degradation. The TIMPs are endogenous MMP inhibitors that regulate and...
MMP-2 and MMP-9. It has been reported that TIMP-3 has mechanical ventilation, hyperoxia in mice and spontaneous enhances the inflammatory response, which leads to sepsis, of interrelationships between MMPs and TIMPs. Lack of TIMP-3, pathological conditions has provided insight into the importance MMP-9, but with different affinities. Furthermore, examination can bind and inactivate various MMPs, including MMP-2 and MMP-9. However, role of TIMP-3 is unclear in the animal model of asthma. The use of anti-inflammatory drugs that reduce MMPs and increase TIMP-3 may be effective against airways remodeling due to acute lung inflammation.

Although sephadex model is extremely rapid and simple, limited information underlying cellular and molecular mechanisms are available. We hypothesized that the MMPs/TIMPs system may be closely involved in granuloma formation in the sephadex model. Therefore, our aim was to study the effect (s) of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) and glucocorticoid receptor (GR) agonist in a sephadex-induced lung inflammation model in rat and correlate it with the regulation of MMPs and TIMPs.

Materials and Methods

Chemicals

Rosiglitazone was obtained from Cadila Healthcare Ltd., Ahmedabad, India. Sephadex® G-200 superfine, dexamethasone and other reagent were obtained from Sigma Aldrich Co., USA.

Animals

Male Wistar rats of 6–8 weeks of old were purchased from the Jackson Laboratory. Rats were housed in individual ventilated cages and given pelleted food (Lab Diet, Purina Mills, India) and water ad libitum in a temperature (25°C) and humidity (45–53%) controlled environment with a 12 h/12 h dark-light cycle. The study was approved by the Institutional Animal Ethics Committee. The experimental procedures were performed in accordance with the guidelines of the committee for the purpose of control and supervision of experiment on animals, India.

Experimental Design

Sephadex G-200 beads (0.5 mg/ml) were suspended in normal saline and soaked at 4°C for 72 h after autoclaving. Animals received 1 ml of sephadex suspension intravenously via the tail vein where as normal control rats received saline only. One hour prior to the sephadex injection, dexamethasone (0.3 mg/kg) and rosiglitazone (10 mg/kg) suspended in 0.5% methycellulose was administered by oral gavages followed by two subsequent doses in 24 h intervals. We have used six animals in each group.

Differential Leucocyte Counts in Broncho-alveolar Lavage Fluid

Rats were administered an overdose of pentobarbital sodium (120 mg/kg i.p.) on day 4. After semi-excision of the trachea, a plastic cannula was inserted, and airspaces were washed with 5 ml of heparin (6 IU/ml) treated saline. After 2 min, the lavage fluid was recovered by gentle aspiration. This operation was repeated 2 more times, and collections were pooled. The fluid phase of the first milliliter of broncho-alveolar lavage fluid (BALF) was centrifuged (4000 rpm for 10 min, 4°C) and the supernatant was frozen at −80°C until cytokine analysis. Remaining pooled portion of BALF was centrifuged (600 g for 10 min, 4°C) and the supernatant fraction discarded and the cells pellet re-suspended in 1 ml of saline. Total white blood cells (WBCs) were counted by coulter counter method using Cell-DYN 3700 (Abbott instruments, USA). A small piece of lower right lung was snap frozen in liquid nitrogen for gene expression and the estimation of hydroxyproline. Rest of the tissue was fixed in 10% formal saline for histological examination.

Broncho-alveolar Lavage Fluid Cytokines Measurement

The concentration of tumor necrosis factor-alpha (TNF-α) in BALF was measured using a commercially available enzyme-linked immuno sorbent assay (ELISA) kit (BD Biosciences, San Diego, USA). Levels of leukotriene B4 (LTB4) and prostaglandin E2 (PGE2) were also measured using specific ELISA kits (R and D systems, Inc., Minneapolis, USA).

Histopathological Analysis

Tissue sections were prepared of the lungs tissues fixed immediately in 10% formal saline. Paraffin-embedded sections (4 μm) of the lung were stained with hematoxylin-eosin and masson’s trichrome stain. The lung histology was assessed by light microscopy.

Gene Expression using Quantitative Reverse Transcription Polymerase Chain Reaction

Lung tissue samples were homogenized in trizol reagent (Invitrogen, Life Technologies, Carlsbad, CA, USA) using a Polytron hand-held homogenizer (Kinemitica, Switzerland) and total RNA was extracted following the manufacturer’s protocol. Quality and quantity of RNA samples were assessed by spectrophotometric analysis. 1 μg of total RNA from each sample was taken for first-strand cDNA synthesis using a high-capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA). An equal amount of cDNA from each sample was taken for quantitative reverse transcription polymerase chain reaction (qRT-PCR) using 2 × fast SYBR green master mixes (QIAGEN) using ABI7300 system. PCR was conducted to amplify target cDNA fragments for MMP-9 and TIMP-3. Primers for MMP-9 and TIMP-3, listed in Table 1, were design from rat sequences. Housekeeping gene ribosomal acidic protein was used with both the genes for normalization of the results. Melting curve analysis was carried out at the end of the qRT-PCR.

Hydroxyproline Assay

Quantitative hydroxyproline assay of lungs was performed at the end of the experiment as an indicator of collagen content. A modification of previously described method was utilized.

Statistical Analysis

Results are expressed as mean ± standard error of the mean. Data were analyzed by one-way ANOVA followed by Tukey’s multiple comparison tests. All analysis was done using GraphPad Prism software version 5.0 (GraphPad Software Inc.,
La Jolla, CA, USA). P < 0.05 was considered to be statistically significant.

Results

Sephadex Challenge Mediates Changes in Cellular Composition in Broncho-alveolar Lavage Fluid

Intravenously injected sephadex led to a significant increase in the WBCs count (neutrophil, eosinophil, monocyte, lymphocyte), compared with saline treated rats. Treatment of rats with rosiglitazone (10 mg/kg, p.o.) or dexamethasone (0.3 mg/kg, p.o.) produced inhibition of the total number of cells in the BALF of sephadex challenged group. Dexamethasone treatment resulted in a significant (P < 0.05) inhibition of the total WBCs count, whereas rosiglitazone was less effective and inhibited only the eosinophils and neutrophils [Table 2].

Alteration of Cytokine and Prostaglandins in Broncho-alveolar Lavage Fluid after Sephadex Challenge

Level of TNF-α in the BALF was increased significantly (P < 0.05) after intravenous (i.v) injection of sephadex as compared to saline challenged animals (25.55 ± 2.9 vs. 5.81 ± 0.9 pg/mL). Oral administration of dexamethasone (0.3 mg/kg) showed significant (P < 0.01) reduction in TNF-α level, which was lowered to 7.46 ± 0.6 pg/mL in the BALF after 3 days treatment whereas rosiglitazone had no effect [Figure 1a]. BALF LTB4 levels were also significantly increased (P < 0.05) in sephadex treated animals when compared with saline treated group (91.75 ± 15.9 vs. 14.4 ± 1.8 pg/mL). Oral administration of only dexamethasone showed significant (P < 0.05) reduction in LTB4 levels, which was lowered to 49.12 ± 4.5 pg/mL, whereas rosiglitazone treatment has no significant effect [Figure 1b]. In this study, we found that there was significant (P < 0.01) elevation of PGE2 levels in sephadex injected animals in the BALF as compared to saline control animals (5508.0 ± 442.8 vs. 155 ± 55.5 pg/mL, P < 0.05). There was a significant reduction in PGE2 (452 ± 75.2 vs. 5508.0 ± 442.8 pg/mL, P < 0.05) in the rosiglitazone treated group as compared to sephadex control animals. Interestingly, 90% inhibition of PGE2 was observed in rosiglitazone treated group whereas dexamethasone treatment showed almost 59% inhibition (2255 ± 555 vs. 5508 ± 442.8 pg/mL, P < 0.05) [Figure 1c].

Histopathological Examination of Lung

Haemotoxylin-eosin stained tissues of sephadex treated rats showed prominent inflammation by infiltration of inflammatory cells around the small vessels and interstitium along with mild interstitial edema. More inflammatory cells were present in the alveolar spaces and infiltrated in the alveolar septa and expanded them. In the rosiglitazone treated animals, a few cells were present in the edematous alveolar spaces where as in dexamethasone treated group lower amounts of inflammatory cell recruitment was observed in the broncho-alveolar spaces [Figure 2]. Based on these results we determined the collagen degradation by sephadex using Masson’s trichrome staining. As an indicator of fibrosis, immature collagen fibers, which appeared green in Masson’s trichrome stain, began to deposit focally around the arterioles, bronchioles and alveolar septae in sephadex challenged animals. We found mild collagen deposition around the basement membrane and less subepithelial fibrosis in the rosiglitazone treated group. However, dexamethasone treatment elegantly maintained the lung integrity or bronchial tissue connectivity that might be due to inhibition of collagen degradation [Figure 2].

Expression of Matrix Metalloproteinase 9 and Tissue Inhibitor of Metalloproteinase 3 in the Lung Tissue

Intravenous administration of sephadex caused up-regulation of MMP-9 expression in lungs which was found to be 3.39 ± 0.19 fold as compared to saline control group. However, we couldn't find any difference in MMP-2 expression between the sephadex challenged and normal control animals (data not shown). For the 1st time we demonstrated down regulation of TIMP-3 (0.28 ± 0.06 fold) in sephadex--induced lung inflammation model. Among the two classes of drugs, dexamethasone significantly (P < 0.05) inhibited the MMP-9 level and up regulated the TIMP-3 expression in lung tissue. Rosiglitazone showed reduction in MMP-9 level, but did not show significant effects on TIMP-3 expression in lung.

### Table 1:

| Gene       | Sense primer: (5’-3’)                                                                 | Antisense primer: (5’-3’)  | bp     |
|------------|-------------------------------------------------------------------------------------|---------------------------|--------|
| RAP        | GACGCTCCGCGAGGATAAGA                                                                | AGACAAAGCCATGTCTAC        | 150    |
| MMP9       | CGACGACGAGCGATTG                                                                   | CTGTGTCAGCCGGATAG         | 128    |
| TIMP3      | CTCTCTTCTCCCTGGCTTCCTCC                                                            | CTCTCTTCTCCCTGCCTTCCTCC   | 350    |

qRT-PCR=Quantitative reverse transcription polymerase chain reaction

### Table 2:

| Normal control | Sephadex control | Rosiglitazone (10 mg/kg) | Dexamethasone (0.3 mg/kg) |
|----------------|------------------|--------------------------|--------------------------|
| WBC count      | 0.83±0.14        | 11.67±0.97*              | 6.31±0.64°               | 1.13±0.12°              |
| Eosinophil count | 0.11±0.02        | 2.89±0.39°              | 1.60±0.25°               | 0.46±0.03°              |
| Neutrophil count | 0.49±0.12        | 7.65±0.77°              | 3.73±0.44°               | 0.28±0.09°              |
| Lymphocyte count | 0.13±0.02        | 0.84±0.20°              | 0.36±0.06°               | 0.15±0.06°              |
| Monocyte count | 0.08±0.03        | 0.51±0.14°              | 0.43±0.08                | 0.15±0.02°              |

Results are expressed as mean±SEM (n=6/group). P<0.05 was considered to be statistically significant. *P<0.05 as compared to normal control vehicle-treated rats, †P<0.05 as compared to Sephadex challenged vehicle treated group. Table depicts the effects of different treatments on WBC count, eosinophil count, neutrophil count, lymphocyte count and monocyte count in BALF after 3 days of treatments. Data were analyzed by one-way ANOVA followed by Tukey’s multiple comparison tests. BALF=Broncho-alveolar lavage fluid, WBC=White blood cell, SEM=Standard error of mean
tissue after normalization with the housekeeping gene ribosomal acidic protein [Figure 3a and b].

**Sephadex Results in Increased Matrix Hydroxyproline Deposition**

Hydroxyproline content in lung homogenates from mice was utilized as an index of matrix collagen content [Figure 4]. Sephadex-induced remodeling was associated with a significant increase in hydroxyproline ($P < 0.05$) when compared to normal mice. Hydroxyproline content was reduced significantly in dexamethasone treated animals whereas it was unaltered by rosiglitazone group when compared with sephadex control animals.

**Discussion**

Corticosteroids are till date the most effective anti-inflammatory medications for the treatment of asthma. Several studies have demonstrated the beneficial effect of glucocorticoids (GCs) in asthma by reducing subepithelial collagen deposition in lung tissues by maintaining the balance between MMPs and TIMP-1.[10] However, major side-effects of steroids limit their therapeutic usefulness.[11] PPAR-gamma a different class of drug may be a substitute for steroids and has been shown to play an important role in the control of inflammatory responses, including within the lung, acting on both immune and nonimmune cells and may help overcome the steroid mediated side effects. PPARs are a member of the nuclear hormone receptor comprises four sub-types: PPAR-alpha, PPAR-beta, PPAR-gamma, and PPAR-delta. PPAR-gamma is highly expressed in white adipose tissue with lower levels in skeletal muscle and liver. It has also been reported that PPAR-gamma expression is increased in asthmatic airways.[12] Bronchial biopsies of untreated asthmatics have considerably more PPAR-gamma staining than nonasthmatic tissue, particularly in mucosal eosinophils and macrophages, airway smooth muscle, and epithelial cells.[13] There is now evidence that activation of PPAR-gamma may regulate ECM deposition that occurs in the airway wall remodelling. The antifibrotic effect of ciglitazone seen in vivo may also be related to regulation of the activity of MMPs or their inhibitors. It has previously been reported that rosiglitazone, a specific PPAR-gamma agonist, inhibits MMP-9 expression in bronchial epithelial cell lines.[14,15] In vivo studies have shown that PPAR-gamma activators and GC agonists can inhibit the release of inflammatory cytokines from airway epithelial cells.[16] Given the growing evidence of the anti-inflammatory effect of these agents, it is speculated that there may also be promising anti-remodelling actions. The current study investigates the anti-remodeling effect of rosiglitazone and dexamethasone in a model of sephadex-induced lung inflammation in rat. Our findings are similar to several earlier studies demonstrating marked accumulation of eosinophils and neutrophils in the airways and BALF.[17] Surprisingly, we found that a single i.v administration of sephadex was sufficient to elicit early changes in airway remodeling. The most striking change in the model was an increase in subepithelial collagen deposition, as determined by morphometric analysis of Masson’s trichrome-stained lung tissue sections and total lung collagen measured by the hydroxyproline analysis. Deposition of collagen in the airway is a key feature of airway remodeling. Our study showed that collagen deposition was associated with up-regulation of MMP-9 and down regulation of TIMP-3 expression in the lung tissues postsephadex challenge. These data demonstrated that both
airway inflammation and airway fibrosis occurred in response to sephadex.

In the present study, we have evaluated two different treatment regimens, PPAR-gamma ligand rosiglitazone and GR agonist dexamethasone and have observed very distinct effects in the lung inflammation model. Treatment with rosiglitazone caused a marked reduction in eosinophils and neutrophils, which are complemented by earlier data demonstrating that rosiglitazone caused reduction in eosinophils and neutrophils in BALF in ovalbumin induced asthma model. However, potent GR agonist dexamethasone produced a characteristically different response and suppressed lymphocytes and monocytes in addition to eosinophils and neutrophils. TNF-α levels are increased in several other inflammatory diseases including asthma and chronic obstructive pulmonary diseases. Previously it has also been demonstrated that sephadex particles increased TNF-α expression in lung epithelial cells and in the BALF. In the present study, treatment with dexamethasone but not rosiglitazone showed reduction of TNF-α in BALF. This effect on TNF-α specifically by dexamethasone might be related to its inhibitory effect on lymphocyte and monocytes infiltration into the alveolar compartment.

In the current study we have also measured PGE2 and LTB4 levels in the BALF from sephadex treated rats, since these PGs have been postulated to have a role in animal model of antigen-induced inflammation and in the inflammatory lung disease. Interestingly for the 1st time we have demonstrated a marked increase in PGE2 levels in the BALF after sephadex challenge. PGE2 plays a key role in numerous physiological and pathophysiological settings as inflammation, and it induces constriction and relaxation of smooth muscles on vascular and nonvascular tissues. The increase in PGE2 level may be one possible explanation for the increased airway hyperresponsiveness due to sephadex. This prostanoid is known to modulate the immune response by regulating the function of cells such as macrophages, T and B lymphocytes. LTB4 also stimulates leukocyte migration, aggregation, adhesion, oxidative burst activity, and degranulation. In the current study, dexamethasone reduced the elevated levels of both PGE2 and LTB4 postsephadex challenge while rosiglitazone treatment was more selective and significantly attenuated the PGE2 levels without altering LTB4 in the BALF. Previously, Hazra et al. also reported a decrease in PGE2 in response to rosiglitazone and pioglitazone. Decrease in cytokine and PGs by the drug treatments may prevent further infiltration of neutrophils and other proinflammatory cells to the site of injury.

Histopathological findings also revealed distinct difference in rosiglitazone and dexamethasone treatment groups. Rosiglitazone treatment reduced the inflammatory changes in response to sephadex beads as observed by H and E stains.
staining. However, dexamethasone significantly inhibited the granulomatous changes, and the infiltration of inflammatory cells into the periphery of the lesion, which corroborated with subepithelial fibrosis in asthma.[24] In the present study, as revealed by the Masson’s trichrome staining, sephadex challenge caused a pronounced deposition of subepithelial collagen degradation product throughout the lungs. However, collagen breakdown product deposition was found to be restricted to the basement membrane in the rosiglitazone treated group, and a mild degradation of collagen was observed in the dexamethasone treated animals.

The MMPs and their inhibitors TIMPs also play a key role in both inflammatory and remodeling pathogenesis. MMPs are particularly potent in degrading basement membrane collagen associated with lung injury in inflammatory processes. MMPs are mainly secreted from the activated neutrophils mononuclear cells. Among the MMPs, gelatinases (MMP-2 and MMP-9) are secreted from the inflammatory cells and degrade basement membrane components and counteract airway wall remodeling caused by fibrosis. In the current study, we examined MMP-2, MMP-9 and TIMP-3 expression in lungs to investigate the molecular mechanism of treatment mediated restoration of lungs architecture. It has been reported that corticosteroids inhibit the production of MMPs and increased expression of TIMP-3 in vitro.[25] We also found suppression of MMP-9 associated with an increase in TIMP-3 expression in lungs tissues of dexamethasone treated animals, which correlated well with the increased neutrophil recruitment. These results suggested that neutrophil recruitment to the respiratory tract and an imbalance between MMP-9 and TIMP-3 might play an important role in sephadex-induced fibrosis. Very recently, it has been reported that TIMP-3 knockout mice exhibit higher expression of pro-inflammatory and lower expression of anti-inflammatory genes.[26] Thus, TIMP-3 may play a key role in maintaining the integrity of the extra cellular matrix in the lungs. In the present study, unlike dexamethasone treatment, we observed a difference in restoration of lung architecture with rosiglitazone. Although the treatment inhibited expression of MMP-9 in lungs from mice exposed to sephadex, it failed to increase TIMP-3 expression and decrease hydroxyproline levels in tissues. This clearly indicates that TIMP-3 expression corroborate well with change in lung architecture.

**Conclusion**

Our result revealed that up-regulation of TIMP-3 was found to have a direct correlation in predicting dexamethasone mediated inhibition of collagen degradation and restoration of alveolar micro-architecture.

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