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EFFECTS OF A PPARγ PARTIAL AGONIST ON LUNG INFLAMMATION

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INTRODUCTION

Respiratory infections have gained significant attention post-COVID-19, highlighting the need for effective and safe treatments. Traditional therapies focused on preventing pro-inflammatory mediators, but resolving inflammation actively turns off the response, preventing tissue damage and restoring homeostasis. Stimulating resolution pathways, rather than just inhibiting inflammation, is crucial. PPARγ agonists play a significant role in anti-inflammatory action by affecting various components of the inflammatory cascade. This study investigated the effect of the glitazone TZD-A1, a PPARγ partial agonist, on neutrophils, macrophages, and lung inflammation models.

MATERIAL AND METHODS

Male Swiss mice (CEUA: 015/22) received TZD-A1 (3, 10, or 30 mg/kg) while control groups received vehicle or dexamethasone (0.5 mg/kg). To assess the involvement of the PPARγ pathway, one group received TZD-A1 (10 mg/kg) plus the antagonist GW9662 (1 mg/kg). Inflammation was induced via intranasal instillation of LPS (4 mg/mL). After 24 hours, lung tissues and bronchoalveolar lavage (BAL) were collected and analyzed for cellularity, MPO, and cytokine secretion. For *in vitro* inflammation evaluation, Human A549 lung cells were stimulated with LPS (10 µg/mL) and treated with TZD-A1 (10 µM), assessing IL-6 secretion. Neutrophils and macrophages were stimulated with LPS (1 µg/mL) and treated with TZD-A1 (0.1, 1, or 10 µM). Evaluations included neutrophil chemotaxis, nitrite and cytokine production, and efferocytosis. A netosis assay was performed with cells stimulated by PMA (100 nM) and treated with TZD-A1. The bioavailability of the compound was analyzed using lung samples from male Swiss mice administered TZD-A1 at different time points.

RESULTS

TZD-A1 was able to reduce the migration of leukocytes, especially neutrophils, to the site of lung inflammation. MPO and inflammatory cytokines (TNF, IL-1β, IL-6 and CXCL-1) had their levels decreased and the levels of the anti-inflammatory cytokine IL-10 increased significantly after TZD-A1 treatment in the lung tissue and BAL. The anti-inflammatory effects obtained in the ARDS model seem to depend on the activation of PPARγ receptor, since the its antagonist GW9662 reversed the TZD-A1 effects. In vitro tests using A549 lung cells showed that the compound does not cause cytotoxicity and reduces IL-6 levels. In neutrophils and macrophages, the TZD-A1 reduced the pro-inflammatory mediator levels, enhanced efferocytosis of apoptotic neutrophils, and reduced chemotaxis and netosis in neutrophils. Pharmacokinetic assay showed a significant bioavailability of oral TZD-A1 in the lung.

CONCLUSIONS

The obtained data shows that TZD-A1 has anti-inflammatory activity, especially in the inflammation of respiratory tract exerting effects on both leukocytes and parenchymal cells.

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