Fourth research

Title

Modeling the Effects of Cypermethrin Toxicity on Ovalbumin-Induced Allergic Pneumonitis Rats: Macrophage Phenotype Differentiation and p38/STAT6 Signaling Are Candidate Targets of Pirfenidone Treatment.

Cells (2023)

ABSTRACT:

Although the classic form of asthma is characterized by chronic pneumonitis with eosinophil infiltration and steroid responsivity, asthma has multifactorial pathogenesis and various clinical phenotypes. Previous studies strongly suggested that chemical exposure could influence the severity and course of asthma and reduce its steroid responsiveness. Cypermethrin (CYP), a common pesticide used in agriculture, was investigated for the possible aggravation of the ovalbumin (OVA)-induced allergic pneumonitis and the possible induction of steroid resistance in rats. Additionally, it was investigated whether pirfenidone (PFD) could substitute dexamethasone, as an alternative treatment option, for the induced steroid resistance. Fifty-six male Wistar albino rats were randomly divided into seven groups: control, PFD alone, allergic pneumonitis, CYP alone, allergic pneumonitis/CYP-exposed, allergic pneumonitis/CYP/dexamethasone (Dex), and allergic pneumonitis/CYP/PFD- treated groups. Allergic pneumonitis was induced by three intraperitoneal OVA injections administered once a week, followed by an intranasal OVA instillation challenge. CYP (25 mg/kg/d), Dex (1 mg/kg/d), and PFD (100 mg/kg/d) were administered orally from day 15 to the end of the experiment. Bronchoalveolar lavage fluid (BALF) was analyzed for cytokine levels. Hematoxylin and eosin (H&E) and periodic acid Schiff (PAS)-stained lung sections were

prepared. Immunohistochemical identification of p38 MAPK and lung macrophages was performed. The inflammatory/oxidative status of the lung and PCR-quantification of the STAT6, p38 MAPK, MUC5AC, and IL-13 genes were carried out. The allergic pneumonitis-only group showed eosinophil-mediated inflammation ($p < 0.05$). Further CYP exposure aggravated lung inflammation and showed steroid-resistant changes, p38 activation, neutrophil-mediated, M1 macrophage-related inflammation ($p < 0.05$). All changes were reversed ($p < 0.05$) by PFD, meanwhile not by dexamethasone treatment. Pirfenidone could replace dexamethasone treatment in the current rat model of CYP-induced severe steroid-resistant asthma via inhibiting the M1 macrophage differentiation through modulation of the STAT6/p38 MAPK pathway.
Keywords: asthma exacerbation; CD86/CD206 immunohistochemistry; environmental triggers; p38/STAT6; Th2/Th1 inflammation