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Title: Effect of doxofylline on LPS-induced leukocyte migration to the lung

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Body: Doxofylline is a xanthine drug that shows bronchodilator and anti-inflammatory activity. However, the precise mechanism of action of doxofylline is unknown and its anti-inflammatory activity has not been widely investigated. Methods: Doxofylline (0.3 mg/kg i.p.) was given -24, -1 and 6 h after LPS (10 µg/mice, i.n.) in Balb/c mice. Lung lavage was performed 24 h later. Lungs were collected for immunohistochemistry staining of ICAM-1 and VE-cadherin expression. Bone marrow cells were collected and stained for the expression of the markers of activation CD11b and CD62L after stimulation with TNF-a and measured by flow citometry. Results: LPS recruited significantly higher number of neutrophils (PMN) to the lung (mean±SEM) compared to saline (saline:0±0 vs LPS:2.8±0.12 x10^6cells/ml, n=9). Doxofylline (Doxo) significantly inhibited the recruitment of PMN (LPS/Doxo:1.02±0.1 x10^6cells/ml, n =8; $p<0.05$ vs LPS alone). Immunostaining demonstrated that doxofylline (0.3 mg/kg) inhibits the expression of ICAM-1, but does not alter the expression of VE-cadherin in the lung vascular tissue (ICAM-1 LPS:34.4±1.2 vs Doxo:19.9±2.6 % mean brightness, p=0.001, n=4). Pre treatment with doxofylline (0.1-10 µM) did not significantly alter the expression of CD11b or CD62L on the surface of bone marrow leukocytes. Conclusion: Doxofylline inhibits LPS-induced inflammation in the lung by regulating the expression of certain adhesion molecules on the surface of the endothelial layer of the lung vasculature.