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Title: Anti-inflammatory activity of doxofylline and theophylline in LPS-induced lung inflammation

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Body: Doxofylline and theophylline are two xanthine drugs that show both bronchodilator and anti-inflammatory actions. Data has suggested that doxofylline has a wider therapeutic window than theophylline 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.) and Theophylline (10 mg/kg, i.p.) were given -24, -1 and 6 h after LPS (10 µg/mice, i.n.) in Balb/c mice. Lung lavage was performed 24 h later. In other experiments, doxofylline (0.3 mg/kg, i.p.) was given -24, -1 and 6 h after injection of LPS (10 µg) into the scrotal sac. Mice were prepared for intravital microscopy 24h later. Results: LPS recruited significantly higher number of neutrophils (PMN) to the lung (mean±SEM) compared to saline (saline:0±0 vs LPS:2.4±0.2 x10^6cells/ml, n =4). Doxofylline (Doxo) significantly inhibited the recruitment of PMN (LPS/Doxo:1.4±0.2 x10^6cells/ml, n =4; $p<0.05$ vs LPS alone). Theophylline (Theo) did not alter the recruitment of PMN in response to LPS (LPS:1.9±0.2 x10^6cells/ml vs LPS/Theo:2.5±0.2 x10^6cells/ml, n=8). Mice showed an accumulation of cells in the tissue (cells/50µm^2) (saline:0±0 vs LPS:9.3±2.5, n=4; $p<0.05$) and higher number of cells rolling (cells x100µm^2) in 30 sec (saline:0.2±0.2 vs LPS:5.3±2.4, n =4, $p<0.05$) 24 h after LPS injection into the scrotal sac. Doxofylline significantly inhibited cell migration in response to LPS (LPS/Doxo:3.1±1.9, n=4; $p<0.05$ vs LPS alone) but significantly increased cell rolling (10.2±3.0, n=4; $p<0.05$ vs LPS alone). Conclusion: Doxofylline significantly reduced cell transmigration in response to LPS, supporting an anti-inflammatory action.