Modeling Physiologic Effects of Chronic Endotoxin Exposure in Mice.

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Introduction: Chronic cotton mill dust exposure in humans results in airflow obstruction that has been attributed to environmental endotoxin. For further study, investigators have used mouse models of chronic endotoxin exposure that require 8–hour exposure protocols that are not universally feasible. We set out to develop a mouse model of LPS–induced chronic airflow obstruction, using once–daily exposure and invasive measures of airway function. *Methods*: C57BL6 mice received 2 mg of nebulized endotoxin (LPS) or control (PBS) daily for 5 days, 4 weeks (5d/wk), or 8 weeks (5d/wk), and mice were then anesthetized and tracheotomized. Central airway resistance (Rn) was measured using a mouse ventilator pre– and post–methacholine challenge, and bronchoalveolar lavage (BAL) fluid was collected. *Results*: Increased Rn was observed at baseline and after methacholine (0.9 to120 mg/ml) in LPS–exposed mice (n=5 mice/group), compared with control (PBS) mice (LPS *vs* PBS Rn after peak methacholine at 5d: 2.8 ± 0.1 *vs* 1.9 ± 0.1; and at 8 wks: 2.6 ± 0.3 *vs* 1.6 ± 0.1 cmH_20/ml/sec; $p<0.05$ for each). Total BAL cell counts were significantly elevated in LPS–exposed mice, (LPS *vs* PBS at 5d: 2.6 ± 0.4$x10^5$ *vs* 1.0 ± 0.2$x10^5$; at 4 wks: 3.6 ± 0.2 $x10^5$ *vs* 1 ± 0.3 $x10^5$; and at 8 wks: 4.0 ± 0.9$x10^5$ *vs* 0.6 ± 0.3$x10^5$; $p<0.05$ for each). Unexpectedly, LPS–exposed mice at 5d exhibited 35±9% BAL neutrophils, which by 8 wks was significantly increased to 42±2% ($p<0.05$). *Conclusion*: Daily inhaled LPS in mice results in increased airway resistance that mirrors airflow obstruction in human occupational exposures. A durable inflammatory response with an increasing percentage of BAL neutrophils over the 8–wk LPS exposure protocol was observed. Future studies will use this model to dissect the persistent inflammatory response and mechanisms underlying lung dysfunction as a result of chronic endotoxin exposure.

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