Attenuation of Nitrogen Mustard Induced Lung Injury by N-Acetylcysteine

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Nitrogen mustard (NM) is a blistering agent developed for chemical warfare agent that causes severe lung injury following exposure. Currently, there are no approved treatments for mustard-induced lung injuries. NM induces oxidative stress in the lung, which is thought to be key in its pathophysiological actions. N-acetyl cysteine (NAC), a precursor to L-cysteine is an antioxidant that reduces oxidative stress by replenishing glutathione. Our study aimed to elucidate the therapeutic potential of NAC in nitrogen mustard-induced lung injury. Male Wistar rats were intratracheally exposed to NM (0.125 mg/kg) and administered NAC (150 mg/kg/day) or vehicle daily beginning 30 minutes post-exposure for 3 days; rats were euthanized 24 h after the last treatment. NM exposure resulted in increased levels of interleukin (IL)-2 and surfactant protein-D (SP-D) in bronchoalveolar lavage (BAL) 3 d post exposure; increases in BAL protein, immunoglobulin M (IgM) and cell content were also noted suggesting lung injury and inflammation. This was associated with increases in expression of pro-inflammatory genes including IL-6 and IL-12 in the lung macrophages along with cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), markers for pro-inflammatory M1 macrophages. Increases in expression of resolution of injury markers including IL-10 and chemokine receptor (CX3CR1) were also upregulated in the macrophages. Treatment of rats with NAC inhibited NM-induced increases in IL-2, SP-D, IgM, cell, and protein levels in BAL. NM-induced expression of IL-6, IL-12, COX-2 and iNOS was also reduced by NAC, along with IL-10 and CX3CR1. These findings suggest that NAC treatment is an effective approach to control acute lung injury induced by mustard vesicants. Supported by R25ES020721, U54AR055073, R01ES004738, and P30ES005022.