Attenuation of Nitrogen Mustard Induced Lung Injury by N-Acetylcysteine

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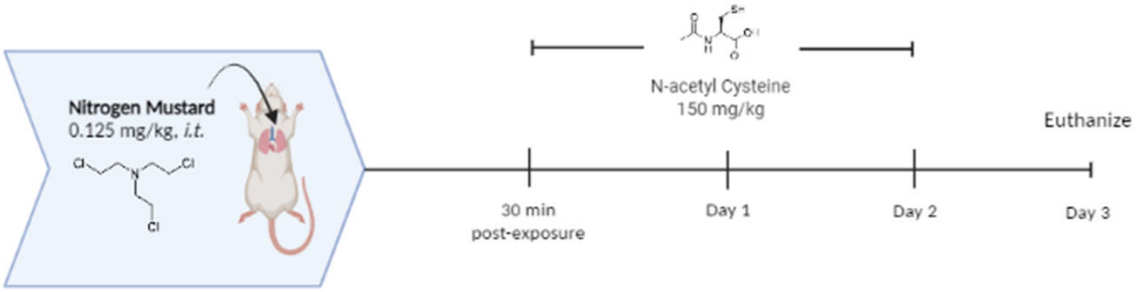
Nitrogen mustard (NM) is a blistering agent developed for chemical warfare agent that causes severe lung injury following exposure. Currently, there are no approved treatments for mustard-induced lung injuries. NM induces oxidative stress in the lung, which is thought to be key in its pathophysiological 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.



Alveolar Macrophages

Bronchoalveolar Lavage Fluid

	Marker	NM	NM+NAC
Pro-inflammatory	COX-2	↑	↓
	iNOS	↑	↓
	IL-6	↑	↓
	IL-12	↑	↓
Anti-inflammatory	IL-10	↑	↓
	CX3CR1	↑	↓

Marker	NM	NM+NAC
IgM	↑	↓
SP-D	↑	↓
IL-2	↑	↓