MECHANISMS OF PULMONARY FIBROSIS: ANTIFIBROTIC ACTIONS OF TETRANDRINE

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The pathogenesis of silicosis involves pulmonary inflammation, granulomas, and pulmonary fibrosis. Alveolar macrophages (AM) are considered to play an important role in the initiation and progression of silicosis. Tetrandrine (TT), an antifibrotic agent, is a bisbenzylisoquinoline alkaloid that has been shown to modulate cellular microtubule structure. The objectives of this research were to assess (1) the interaction of TT with AM, (2) the mechanism of TT action on silica-induced macrophage activation, (3) the antifibrotic effect of TT on silica-induced pulmonary fibrosis in rats. TT was shown to bind only to viable AM in a concentration- and temperature-dependent manner. TT effectively inhibited stimulant-induced AM respiratory burst and the release of proinflammatory cytokines, IL-1 and TNF-α. Binding of TT to AM was blocked by microtubule-modifiying agents such as vinblastine and taxol, which also depressed the inhibitory action of TT on AM production of reactive oxygen species and cytokines in response to stimulant activation. These data suggested that TT binds to AM though macrophage cytoskeletal systems and effectively inhibits stimulant-induced activation of AM. The inhibitory effect of TT treatment on the development of pulmonary fibrosis was investigated in rats exposed to intratracheal silica. TT was administered either orally or through the tail vein. Pulmonary inflammation, lung damage, and fibrosis were assessed by monitoring alveolar cell differentials, acellular lactate dehydrogenase (LDH), phospholipids (PL) and protein content, and collagen synthesis. Macrophage activation was monitored by measuring reactive oxygen species generation and inflammatory mediators, i.e., IL-1, TNF-α and TGF-β secretion. TT treatment resulted in a marked reduction of the acellular LDH, PL and protein content, a significant inhibition of inflammatory mediators released from AM, and a substantial decrease in lung collagen formation in comparison to silica-exposed non-treated rats. The inhibitory effect of TT treatment on silica-induced granulomas and fibrosis in the lung was further confirmed by histological examinations of lung tissues. These studies indicate that AM play a central role in silica-induced pulmonary injury and fibrosis, and that tetrandrine, by its ability to inhibit macrophage activation in responses to silica, reduces silica-induced inflammatory injury and fibrotic development.

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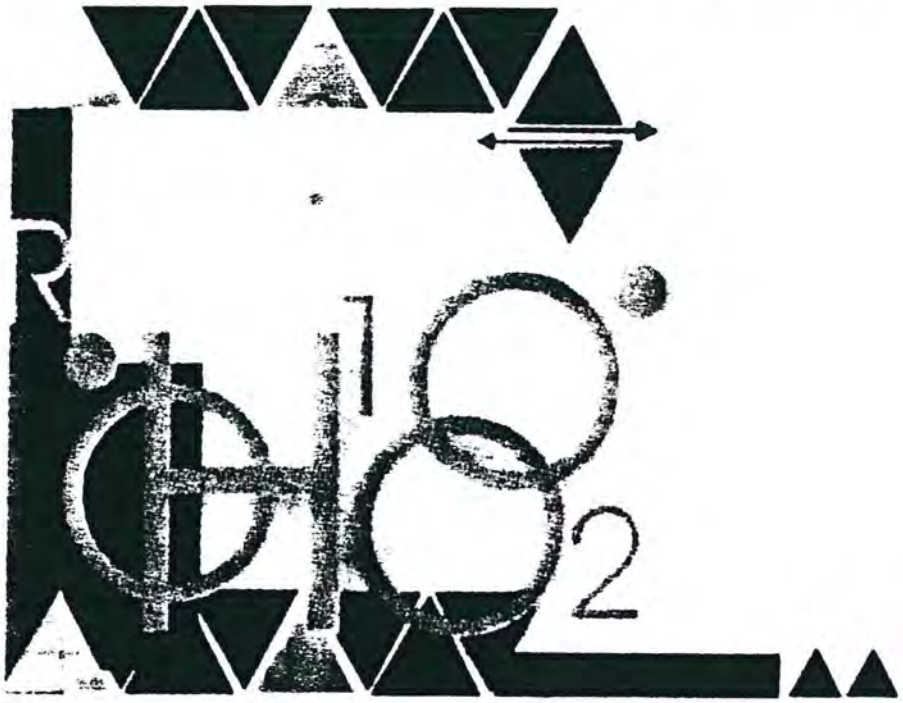

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