ATTENUATION OF ACUTE INFLAMMATORY EFFECTS OF SILICA IN RAT LUNG BY 21-AMINOSTEROID, U74389G

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Abstract—Chemical alteration of the glucocorticoid, methylprednisolone, has led to the introduction of a new class of compounds called the 21-aminosteroids (21-ASs). The purpose of this study was to investigate the effect of the 21-AS, U74389G, on silica-induced acute lung injury. Male Fischer 344 rats were treated intraperitoneally with saline or U74389G in a total dose of 15 mg/kg divided into three injections of 5 mg/kg separated by 4 h. Following the first treatment, animals from the two groups were intratracheally instilled with silica (10 mg/100 g body wt in 0.5 ml of saline) or saline vehicle (0.5 ml). Twenty-four hours after the instillations, bronchoalveolar lavage (BAL) was performed. In the animals not receiving U74389G, marked increases in total protein, β-glucuronidase, and lactate dehydrogenase (LDH) activities and number of neutrophils (PMNs) were demonstrated in the BAL fluid of the silica-treated animals compared to their controls. Silica also caused dramatic increases in the luminol-dependent chemiluminescence (CL) of lung tissue and BAL cells. The CL reaction was decreased by superoxide dismutase (SOD) and N-nitro-L-arginine methyl ester hydrochloride (L-NAME), a nitric oxide (NO) synthase inhibitor. In animals treated with U74389G, there was attenuation of the silica-induced increases in biochemical, cellular, and chemiluminescent indices of damage. This study demonstrates that U74389G significantly reduces acute lung injury caused by the intratracheal instillation of silica, and this drug may be of potential value for treatment of lung diseases in which damage caused by reactive oxygen species has been implicated.

INTRODUCTION

Glucocorticoids (prednisone, methylprednisolone, and dexamethasone) are very useful agents for treating inflammation (1, 2); however, they have some significant side effects that are related to both dosage and duration of administration (3). They suppress the hypothalamic–pituitary–adrenal axis, decrease resistance
to infection, induce hyperglycemia, and are immunosuppressant agents. Due to the seriousness of these adverse effects, the use of glucocorticoids for the treatment of inflammatory conditions is very limited.

The modification of the basic structure of methylprednisolone has led to the introduction of a new class of compounds, 21-aminosteroids (21-ASs). This class of drugs was originally designed as iron-dependent inhibitors of lipid peroxidation (4). These new compounds have been found to improve upon the efficacy of glucocorticoid steroids without exerting their unwanted side effects (5). These 21-ASs have demonstrated therapeutic effects in acute central nervous system trauma (6–8), hypoxia–ischemia in the brain (9), intestinal and renal reperfusion injury (10, 11), and burn injury (12), as well as many other conditions.

The inhalation of silica particles results in activation of the phagocytic alveolar macrophages, which is followed by a severe, acute inflammatory response, damage to the respiratory epithelium and interstitial matrix, and the eventual development of fibrosis (13). The cytotoxic activity of silica appears related to the release of reactive oxygen species, hydrolytic enzymes, and other inflammatory factors from pulmonary phagocytes [resident alveolar macrophages and recruited neutrophils (PMNs)] after stimulation by the inhaled particles (14).

The 21-ASs have also been shown to be effective in the treatment of hypoxic lung injury in rats (15). Thus, these compounds are of potential value in treating lung diseases in which oxidant damage has been implicated and may be of some use in alleviating some of the pulmonary damage that is associated with exposure to silica.

The objective of this study was to evaluate the effectiveness of U74389G, a 21-AS, in attenuating the acute silica-induced pneumotoxic response. In the assessment of lung damage for this study, a variety of cellular and biochemical indices of pneumotoxicity were measured within the acellular bronchoalveolar lavage (BAL) fluid. Previous studies have indicated analysis of the BAL fluid is a sensitive means of characterizing acute inflammatory responses within the lungs (16, 17). In addition, the luminol-dependent chemiluminescence (CL) of the cells and the lung tissue recovered from exposed animals also was measured. CL, the emission of light, is associated with the release of reactive forms of oxygen from phagocytic cells when they are stimulated. With CL, biochemical, and cellular analyses, it was then possible to investigate the use of U74389G in the prevention of silica-induced oxidant lung damage.

MATERIALS AND METHODS

Chemicals and Reagents The silica (α-quartz) particles were originally from Pennsylvania Sand and Glass Co., Pittsburgh, Pennsylvania. The diameter size of the particles was 5 μm or less, with silica content 98.05%. The 21-AS, U74389G, was kindly provided by Dr. David C. Zim-