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Title: The adenosine A2B receptor antagonist GS-6201 reduces small artery muscularization and plasma endothelin-1 in a short term cigarette smoke exposure model

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Body: Adenosine plays an important role in the development and progression of lung injury with increased levels of adenosine and expression of A2B receptors. The A2B antagonist GS-6201 has shown anti-inflammatory effects in an acute model of cigarette smoke- induced lung injury. We have previously shown that exposure to cigarette smoke induces small artery remodeling and increased pulmonary arterial pressures in the guinea pig. Because A2B adenosine receptors are highly expressed in the pulmonary vasculature, we hypothesized that the A2B antagonist GS-6201 may prevent this remodeling. We exposed groups of six guinea pigs to 5 cigarettes per day 5 days per week for 4 weeks; groups were given oral vehicle or GS-6201 in doses of 3, 10 and 30 mg/kg (QD) 2 hours prior to smoke exposure, and a group was exposed to room air. 24 hours after final exposure, the animals were anesthetized and pulmonary arterial pressure was measured directly. One lung lobe was lavaged, and inflammatory cell counts obtained, one lobe was inflated with agarose for morphometric analysis of muscularization of the small pulmonary arteries. Plasma was obtained for measurement of endothelin-1 (ET-1. We found that cigarette smoke induced a non-significant increase of the pulmonary arterial pressure, but a significant increase in small arterial muscularization that was reduced by GS-6201 in a dose-dependent manner. Plasma ET-1 was increased by smoke exposure, and significantly decreased in a dose-dependent manner by GS-6201 as well. Our data suggest that adenosine receptor A2B antagonists may prevent the development of COPD associated pulmonary hypertension.