GLYCOGEN SYNTHASE KINASE-3β INHIBITION ATTENUATES THE DEVELOPMENT OF BLEOMYCIN-INDUCED LUNG INJURY

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Glycogen synthase kinase-3 (GSK-3) is a ubiquitous serine-threonine protein kinase that participates in a multitude of cellular processes and has recently been implicated in the pathophysiology of a number of diseases. The aim of this study was to investigate the effects of TDZD-8, a potent and selective GSK-3β inhibitor, on the development of lung injury caused by administration of bleomycin (BLM). Mice subjected to intra-tracheal administration of BLM developed significant lung injury characterized by marked neutrophil infiltration and tissue edema. An increase in immunoreactivity to nitrotyrosine, iNOS, TNF-α and IL-1β was also observed in the lungs of BLM-treated mice. In contrast, administration of BLM-treated mice with TDZD-8 (1 mg/kg daily) significantly reduced (I) the degree of lung injury, (II) the increase in staining (immunohistochemistry) for myeloperoxidase (MPO), nitrotyrosine, iNOS, TNF-α and IL-1β and (III) the degree of apoptosis, as evaluated by Bax and Bcl-2 immunoreactivity and TUNEL staining. Taken together, these results clearly demonstrate treatment with the GSK-3β inhibitor TDZD-8 reduces the development of lung injury and inflammation induced by BLM in mice.