β2-Agonists Promote Influenza A-Induced Lung Injury Via Increased Il-6 Release From Alveolar Macrophages

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Rationale: β_2-agonists have been proposed as a promising therapy in ARDS due to their ability to improve lung edema clearance via β_2 ARs on alveolar epithelial cells. However, recent clinical trials evaluating the role of β_2-agonists as a therapy for ARDS have reported unexpected harm. β_2-agonists not only failed to improve outcomes but also led to an unexpected increase in mortality when administered systemically. In a model of particulate matter exposure, we have recently found that β_2-agonists worsened lung inflammation by promoting IL-6 release from alveolar macrophages. Based on these findings, we hypothesized that the unexpected outcomes seen with β_2-agonists may be explained by their "off-target" effect of on alveolar macrophages.

Methods: Wild-type (C57BL/6J) mice, and mice lacking β_2-adrenergic receptors (β_2ARs) globally ($\beta_2AR^{-/-}$) or specifically in macrophages (LysM-Cre;$\beta_2AR^{fl/fl}$) or alveolar epithelial cells (SPC-Cre;$\beta_2AR^{fl/fl}$) and controls ($\beta_2AR^{fl/fl}$) as well as IL-$6^{-/-}$ mice were intratracheally infected with an influenza A virus (A/WSN/33 [H1N1]) to induce acute lung injury. To evaluate the effects of β_2-agonists on acute lung injury, mice were treated with either a long-acting β_2-agonist, formoterol or control vehicle. We assessed the influenza A-induced morbidity (weight loss) and mortality as well as IL-6 in bronchoalveolar lavage fluid.

Results: Compared with control treatment, formoterol caused an exaggerated IL-6 response, and weight loss and shortened survival in wild-type mice. β_2-agonists promoted influenza A-induced IL-6 release from primary murine and human macrophages ex vivo. In contrast, $\beta_2AR^{-/-}$ mice had lower levels of IL-6, and improved survival after influenza infection. Similarly, mice lacking β_2AR specifically in macrophages (LysM-Cre;$\beta_2AR^{fl/fl}$) had improved survival while animals lacking β_2AR in alveolar epithelial cells (SPC-Cre;$\beta_2AR^{fl/fl}$) had worse survival compared to controls $\beta_2AR^{fl/fl}$. Lastly, IL-$6^{-/-}$ had improved survival after influenza compared to wild-type mice .

Conclusions: β_2-agonist therapy worsens influenza A-induced lung injury via an exaggerated IL-6 release from alveolar macrophages. The effects of β_2-agonist on alveolar macrophages to promote IL-6 outweigh their beneficial effects on alveolar epithelial cells to promote alveolar fluid clearance. Loss of β_2AR signaling in alveolar macrophages improves IL-6 levels and mortality suggesting a role for endogenous catecholamines in the pathogenesis of lung injury. β-blockers may serve as a potential therapy to improve worsening of influenza A-induced lung injury by "normalizing" an exaggerated IL-6 response.

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