

Tavares LP, Garcia CC, Vago JP, Queiroz-Junior CM Galvão David BA, Rachid MA, Silva PMR, Russo RC, Teixeira MM, Sousa LP. (2015). Inhibition of PDE4 during pneumococcal pneumonia reduces inflammation and lung injury in mice. *American Journal of Respiratory Cell and Molecular Biology*, 2015 Dec 17. [Epub ahead of print].

RATIONALE:

Pneumococcal pneumonia is a leading cause of mortality worldwide. The inflammatory response to bacteria is necessary to control infection but may also contribute to tissue damage. Phosphodiesterase-4 (PDE4) inhibitors, such as rolipram (ROL), effectively reduce inflammation. Here, we examined the impact of rolipram in a pneumococcal pneumonia murine model.

METHODS:

Mice were infected intranasally with 10⁵-10⁶CFU of *S. pneumoniae*, treated with rolipram (ROL) in a prophylactic or therapeutic schedule in combination or not with the antibiotic ceftriaxone. Inflammation and bacteria counts were assessed and ex vivo phagocytosis assays were performed.

RESULTS:

ROL treatment during *S. pneumoniae* infection decreased neutrophil recruitment into lungs and airways and reduced lung injury. Prophylactic ROL treatment also decreased cytokines levels in the airways. Although modulation of inflammation by ROL ameliorated pneumonia, bacteria burden was not reduced. On the other hand, antibiotic therapy reduced bacteria without reducing neutrophil infiltration, cytokine level and lung injury. Combined ROL and ceftriaxone treatment decreased lethality rates and was more efficient in reducing inflammation, by increasing pro-resolving protein Annexin A1 expression, and bacterial burden by enhancing phagocytosis. Lack of Annexin A1 increased inflammation and lethality induced by pneumococcal infection.

CONCLUSION:

These data show that immunomodulatory effects of PDE4 inhibitors are useful during severe pneumococcal pneumonia and suggest their potential benefit as adjunctive therapy during infectious diseases.

KEYWORDS:

PDE4; *Streptococcus pneumoniae*; immunomodulation; inflammation