

## THE ROLE OF CRH IN THE LUNG DURING PNEUMOCOCCAL INFECTION

**Brittney N. Burnley\***, **Preston I. Burnley\*\***, **Dong-Ming Su\*\***, **Harlan Jones\***

*\*Department of Molecular and Medical Genetics, \*\* Department of Cell Biology and Immunology, UNT Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, Texas 76107*

Complications from respiratory pneumonia, mainly caused by *Streptococcus pneumoniae* (*S. pneumoniae*), account for the majority of deaths due to respiratory disease worldwide. Treatment with antibiotics is the standard protocol in eliminating *S. pneumoniae* during infection. However, suppression of inflammatory responses, through glucocorticoids, is also used as an adjunctive therapy during severe infection. Glucocorticoids (GCs) are central mediators of immune suppression and are the primary pharmacologic treatment used to reduce inflammatory responses (IR) in patients with severe bacterial pneumonia. GC treatment however, remains controversial due to inconclusive evidence in reducing mortality amongst at risk populations. Cortisol is an important human GC, whose release is regulated by Corticotropin Releasing Hormone (CRH), a neuropeptide produced primarily by the hypothalamus that mediates adaptive physiological responses. Regulation by CRH is typically involved in controlling immune and IR through cortisol, but has been found to have direct impact within inflamed tissues through ligation with two cellular receptors, CRH-R1 and CRH-R2. Though they provide total immune suppression preventing extensive tissue damage, a problem arises with treatment because they leave the host prone to secondary infections which they are unable to combat due to the actions of the GCs. Therefore, a gap remains in the ability to maintain host immune defenses to facilitate clearance of the pathogen, particularly in instances of ineffective antibiotic treatment caused by bacterial resistance. Therefore, the development of approaches that dampen excessive inflammatory responses without jeopardizing the host may hold promise for reducing risk of mortality due to sepsis. The current study tested the effects of CRH and CRH-R1 antagonist, Antalarmin (ANT) administration, in ICR (CD1) mice subjected to  $1 \times 10^5$  colonies forming units (CFUs) of *S. pneumoniae*. All experimental groups were compared to the experimental group receiving Dexamethasone (DEX), which is the pharmacological glucocorticoid analogue currently used in clinical settings. Survival studies were conducted to determine the effect that treatment has on overall survival, after treatment at 18 hours. Lung tissue and total blood was analyzed by CFUs to determine bacterial load 24 hours after infection and treatment (18 hours). Additionally lung tissue was analyzed via H&E to determine changes in lung pathology. Results of survival indicated that when mice were administered CRH, they had a significant increase in survival when compared to the infection only, ANT, and DEX groups. These findings suggest that CRHR1 plays a role in host defenses against pulmonary *S. pneumoniae* infection and may hold promise as a target to control disease mortality as an alternative approach to glucocorticoids.

Keywords: *Streptococcus pneumoniae*, lung, corticotropin releasing hormone