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Glutamine pretreatment alters cytokine levels in Corticotropin-Releasing Hormone- deficient (*Crh-/-*) mice during LPS-induced systemic inflammation

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INTRODUCTION

Glutamine (GLN) has been shown to protect against inflammatory injury and illness in experimental and clinical settings. The mechanism of this protection is unknown; however, laboratory and clinical trial data have indicated a relationship between GLN-mediated protection and enhanced heat shock protein 70 (HSP70). Heat Shock protein (HSP) expression is vital to cellular and tissue protection after stress or injury. Especially, the 70-kDa heat shock protein (HSP70) family is a group of proteins that are critical for protein assembly, folding, and transport. Glucocorticoids modulate the synthesis and expression of HSP70.

Aim of the present work was to study the GLN-mediated effect on HSP70 in glucocorticoid deficient animals. Hypothalamic Corticotropin Releasing Hormone (CRH), a major mediator of the stress response, is involved in the inflammatory response by exerting indirect anti-inflammatory effects via stimulation of glucocorticoid release, as well as, potent direct proinflammatory effects in a plethora of tissues. Previous studies have shown that mice deficient for *Crh* (*Crh-/-* mice) have also insufficient basal and stress-induced glucocorticoid release. In addition, *Crh-/-* mice show 2-3x higher plasma cytokine levels following LPS-induced systemic inflammation and increased mortality.

METHODS

For our studies we used adult (8-12 weeks old) male wild type (*Crh+/+*) and *Crh-/-* mice. GLN (750 mg/kg body weight) was administered intraperitoneally 45 min before the injection of LPS (80 μg/mouse). The control groups received only GLN at the same dose. Blood and lung tissue were collected 16 hr following the injection of LPS and were immediately frozen and stored at -80 °C. Plasma and lung TNFα and IL-6 concentrations were measured by ELISA.

RESULTS AND DISCUSSION

Our results showed that GLN administration decreased plasma IL-6 levels in LPS-treated *Crh -/-* mice, while it had no effect on plasma IL-6 levels in LPS-treated *Crh+/+* mice. In addition, GLN pretreatment significantly decreased lung IL-6 expression at 16 hr in both genotypes. Similarly, GLN administration significantly attenuated (50%) the plasma concentration of TNFα in *Crh -/-* mice compared to the group that received only LPS. However, *Crh+/+* mice showed no significant difference in the lung TNFα levels with or without GLN pretreatment. In order to test if the effect of GLN in both genotypes is mediated by HSP70, we measured the lung levels of HSP70 in LPS-treated *Crh+/+* and *Crh -/-* mice with or without pre-administration of GLN. To our surprise GLN did not alter HSP70 protein expression in LPS-treated *Crh-/-* mice. However, GLN significantly induced (4x) HSP70 protein levels in LPS-treated *Crh+/+* mice. In summary our data provide evidence that GLN can protect *Crh-/-* mice from LPS-induced systemic inflammation by lowering plasma and tissue cytokine levels. The mechanism through which GLN attenuates the cytokine response in LPS-treated *Crh -/-* mice is under investigation.