# Histamine has a contributory role in promoting organ injury in sepsis: experimental studies using knockout mice of histamine-related genes

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## ABSTRACT

Background: Histamine assumes a critical role as a major mediator of many disorders with inflammation and immune reactions. However, direct evidence has not been provided showing the involvement of histamine in the development of multiple organ dysfunction or failure in sepsis. The goal of the present study was to assess the response to sepsis caused by cecal ligation and puncture (CLP) in histamine decarboxylase knockout (HDC-/-) mice and histamine H1-/H2- receptor double knockout (H1R-/-/H2R-/-) mice.

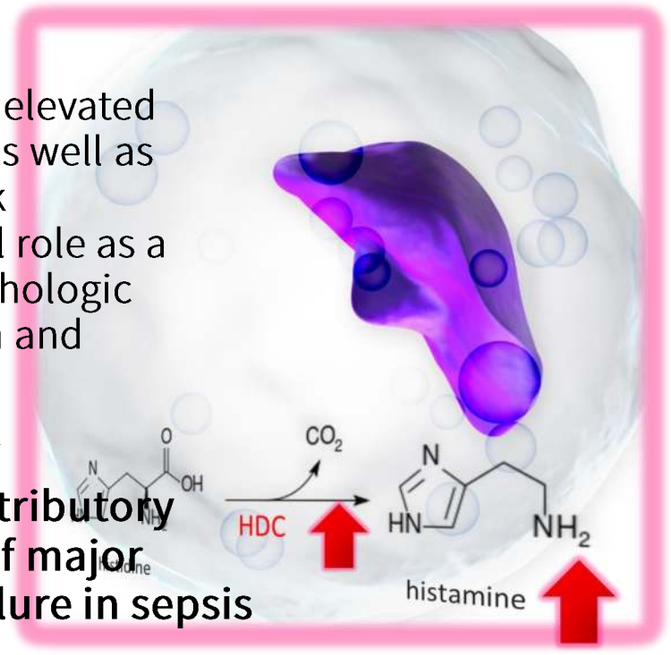
Materials and Methods: H1R-/-/H2R-/- mice were generated by crossbreeding H1-receptor null mice and H2-receptor null mice. Polymicrobial sepsis was induced by CLP in HDC-/- mice, H1R-/-/H2R-/- mice, and their littermate wild type (WT) mice.

Results: Knockout mice of histamine-related gene showed lower levels of serum aminotransferase activity, serum creatinine, and serum and tissue pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and MCP-1) than WT mice when the animals were rendered septic by CLP. Histopathological examinations showed significantly reduced acute lung, liver, and kidney injury after CLP in HDC-/- and H1R-/-/H2R-/- mice. The histamine-mediated development of major end-organ injury was associated with an increase in the nuclear factor-kB signaling pathway.

## BACKGROUND

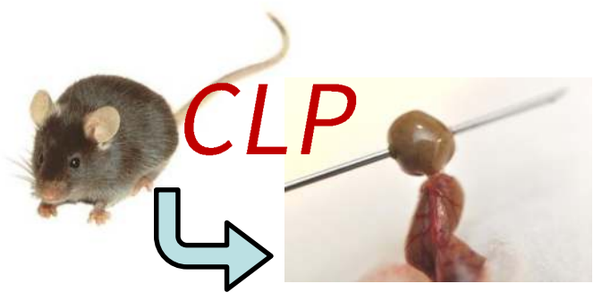
- Plasma histamine levels are elevated in animal models of sepsis as well as in patients with septic shock
- Histamine assumes a critical role as a major mediator of many pathologic disorders with inflammation and immune reactions

**Histamine may play a contributory role in the development of major organ dysfunction and failure in sepsis**




## MATERIALS & METHODS

Use Knockout Mice of Histamine-Related Genes




Genetic Background: C57BL/6J

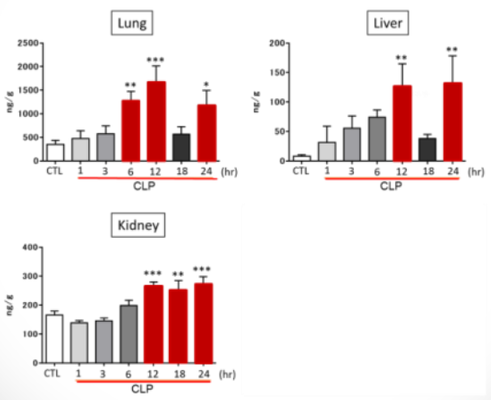
Male, 8-10 Weeks Old

HDC Knockout ($HDC^{-/-}$)

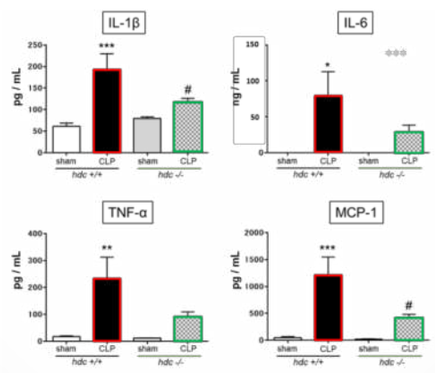
Histamine H1-/H2-Receptor Knockout ($H1R^{-/-}/H2R^{-/-}$)

## RESULTS

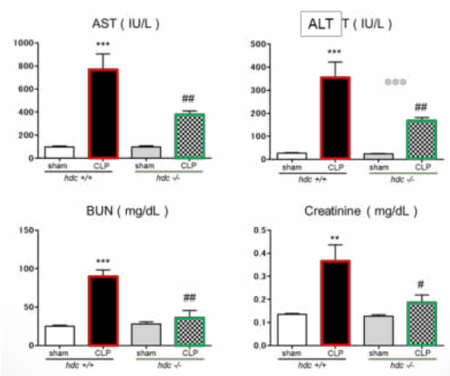
### Tissue Histamine Concentrations in WT Mice after CLP



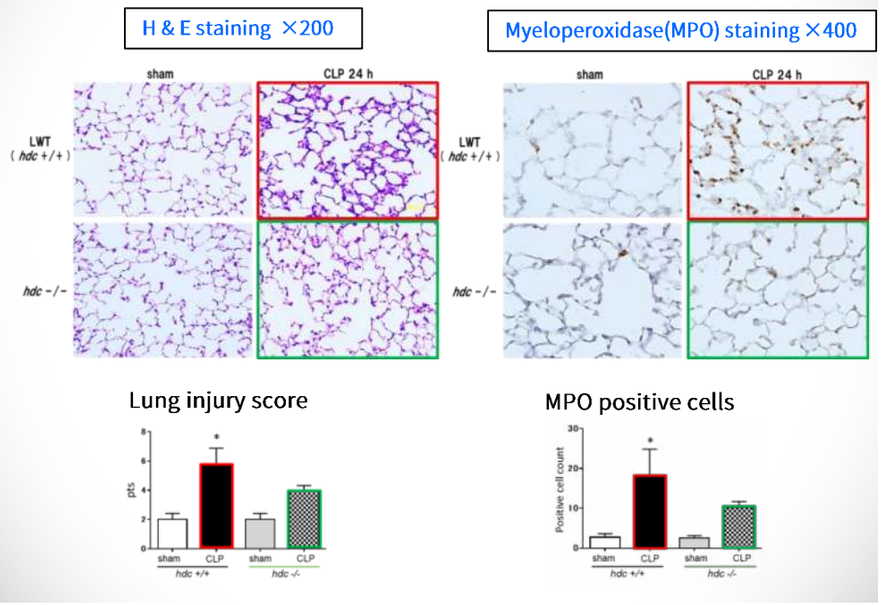

### Reduced Blood Levels of Proinflammatory Cytokines in HDC-/- Mice after CLP



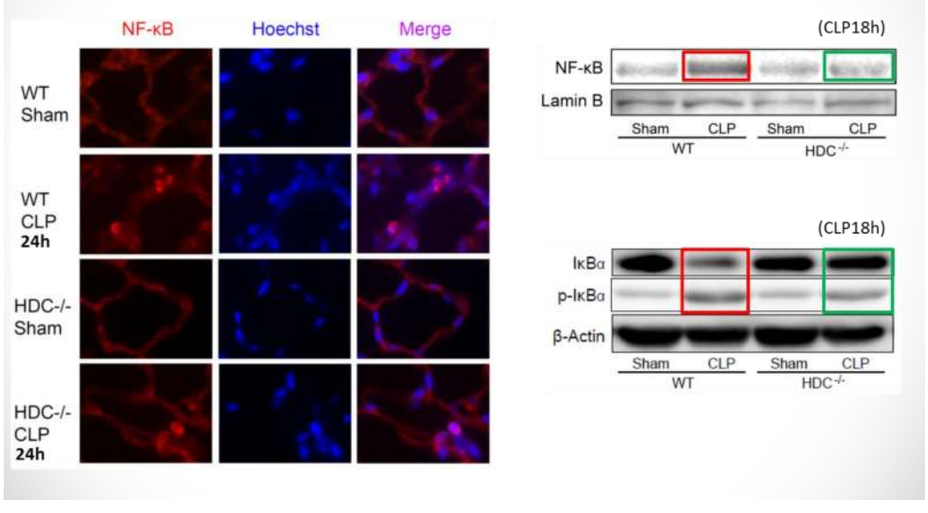

### Blood Biochemistry in HDC-/- Mice after CLP



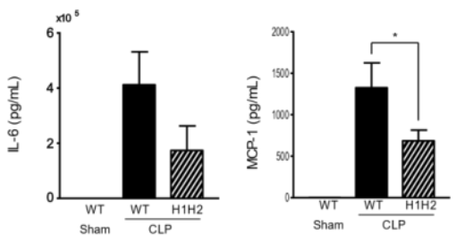

### Lung Histopathological Changes in HDC-/- Mice after CLP



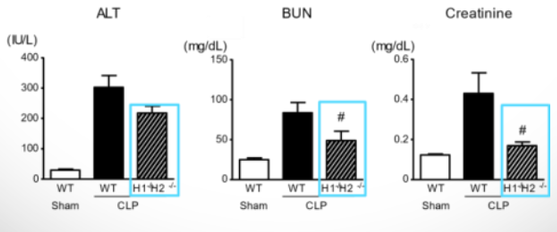

### NF-kB Activation in Lungs of HDC-/- Mice after CLP



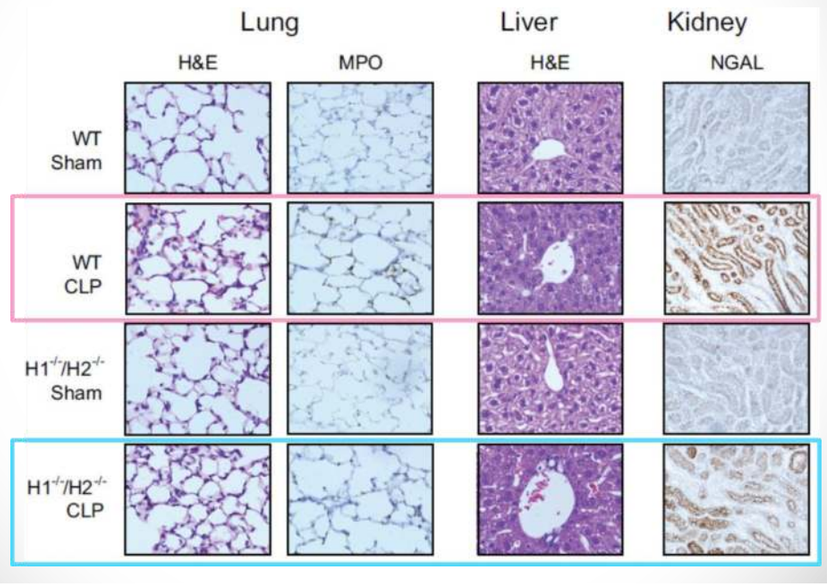

### Reduced Blood Levels of IL-6 and MCP-1 in H1R-/-/H2R-/- Mice after CLP




### Blood Biochemistry in H1R-/-/H2R-/- Mice after CLP




### Reduced Histological Derangements of Lungs, Liver & Kidney in H1R-/-/H2R-/- Mice after CLP




## CONCLUSIONS

These results establish that endogenous histamine acting on H1- and H2- receptors is identified as an aggravating mediator to contribute to the development of major end-organ injury in sepsis. These results also suggest that the validity and feasibility of the use of histamine receptor antagonists to septic organ injury.

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