The intradermal LPS challenge as potential in vivo inflammasome model

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Introduction

Processing of pro-interleukin (IL)-1β and IL-18 is regulated by multiprotein complexes, known as inflammasomes. Increased IL-1β and IL-18 production and signaling are implied as key processes in the pathophysiology of various diseases ranging from autoimmune diseases to metabolic disorders and neurodegenerative diseases. Pharmacological control of IL-1β and IL-18 production is regarded to be a promising therapeutic approach.

Aims

To develop and characterize an in vivo human inflammasome challenge for future application in clinical pharmacology studies with novel compounds modulating inflammasome activity.

Methods and results

Ex vivo experiments

- Healthy donors, whole blood
- Incubation LPS, ATP and LPS+ATP
- Cytokine production in culture supernatant

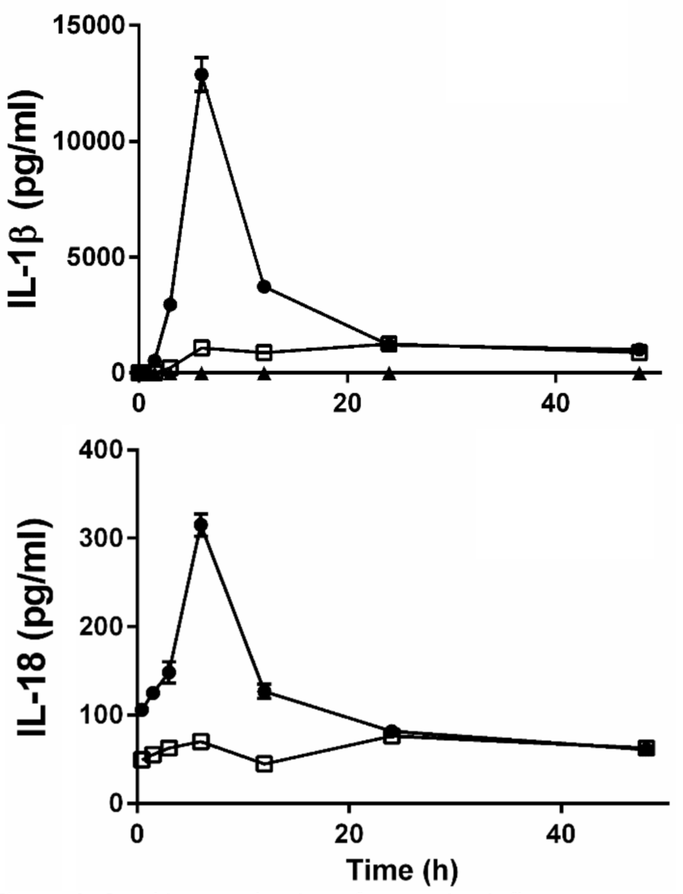

Figure 1. Cytokine production after ex vivo inflammasome challenge (n = 1). Triangle: ATP, Square: LPS, Circle: LPS+ATP. X-axis: Incubation time. Data are expressed as mean±%CV of duplicate conditions of one experiment.

Intravenous LPS challenge

- Healthy volunteers
- Intravenous LPS administration (2 ng/kg)
- Circulating cytokines in blood

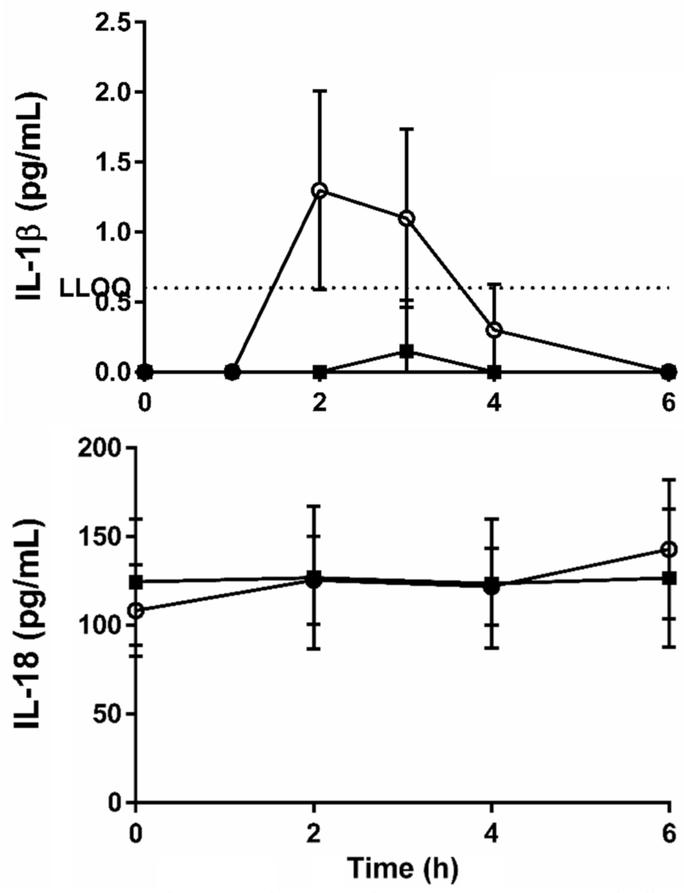

Figure 2. Cytokine production after intravenous LPS challenge. Circle: LPS, Square: Placebo. X-axis: Time after LPS administration. Data are expressed as mean±SD.

Intradermal LPS challenge

- Healthy volunteers
- Intradermal LPS administration (10 ng/injection)
- Local cytokines and ASC in suction blister exudate

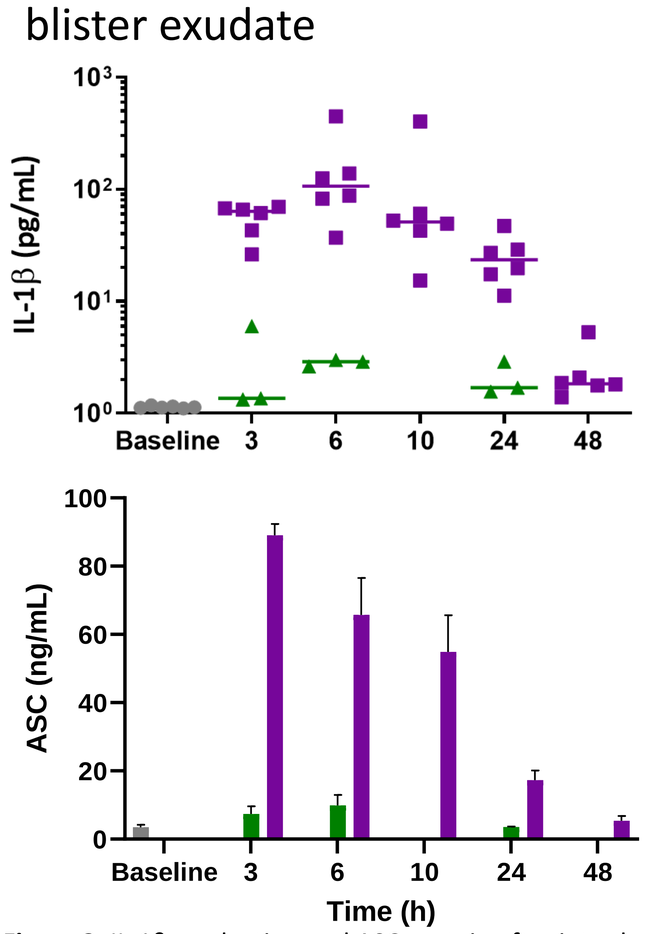

Figure 3. IL-1β production and ASC protein after intradermal LPS challenge. Grey: None, Green: Placebo, Purple: LPS. X-axis: Time after LPS administration. (Top figure) Data are expressed as individual data points and medians. (Bottom figure) Data are expressed as mean±SEM.

Conclusions

Whereas an intravenous LPS challenge does not drive a significant IL-1β response, an intradermal LPS challenge does. Inflammasome activation by LPS probably requires a static environment, as also supported by ex vivo whole blood IL-1β production.

The in vivo intradermal LPS challenge may be a valuable model for future clinical trials investigating the effects of inflammasome inhibitors.

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