Human *ex vivo* and *in vivo* models for inflammasome activation

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Background

Processing of pro-interleukin (IL)-1β and IL-18 is regulated by multiprotein complexes, known as inflammasomes. This process generates bioactive IL-1β and IL-18, two cytokines with potent pro-inflammatory effects. Increased IL-1β and IL-18 production and signaling are implied as key processes in the pathophysiology of various diseases ranging from autoimmune diseases (arthritis, atherosclerosis) to metabolic disorders (diabetes mellitus) and neurodegenerative disease (Alzheimer's). Pharmacological control of IL-1β and IL-18 production is regarded to be a promising therapeutic approach.

Aim

Development and characterization of human inflammasome challenges that may support the clinical development program of future investigational compounds suppressing inflammasome activity and/or IL-1β and IL-18 production.

Methods

Ex vivo experiments	Intravenous LPS challenge	Intradermal LPS challenge
Healthy donors, blood cultures	Healthy volunteers	Healthy volunteers
Incubation with LPS and ATP	IV LPS administration (2 ng/kg)	ID LPS administration (10 ng/injection)
Cytokine release in culture supernatant	Circulating cytokines (blood)	Local cytokines (suction blister exudate)

Results

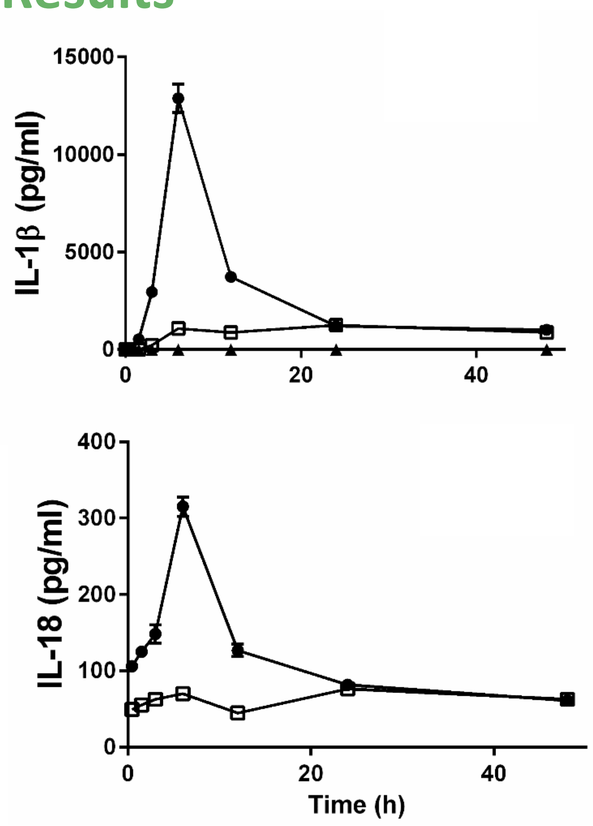

Figure 1: Cytokine production upon ex vivo inflammasome challenge. Square: LPS, triangle: ATP, circle: LPS+ATP. X-axis: incubation time.

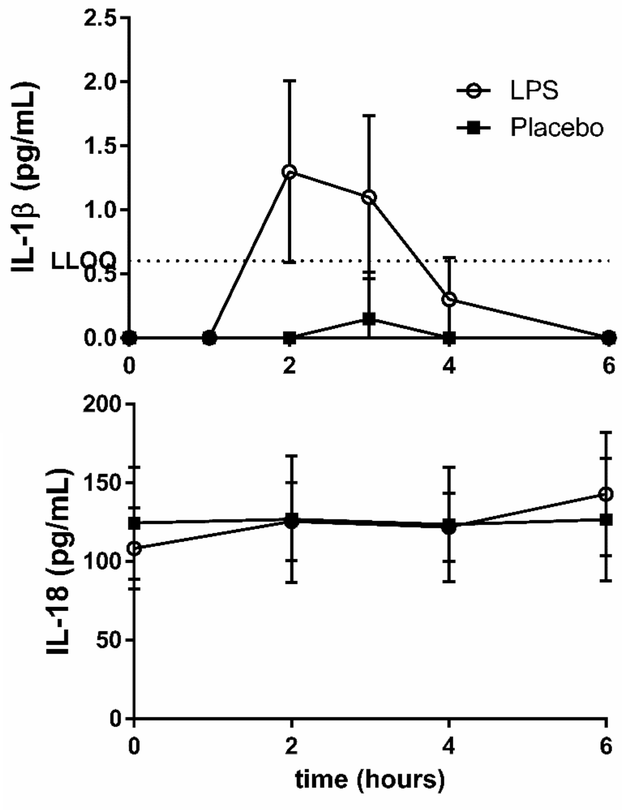

Figure 2: Cytokine production after intravenous LPS challenge. X-axis: time after LPS administration.

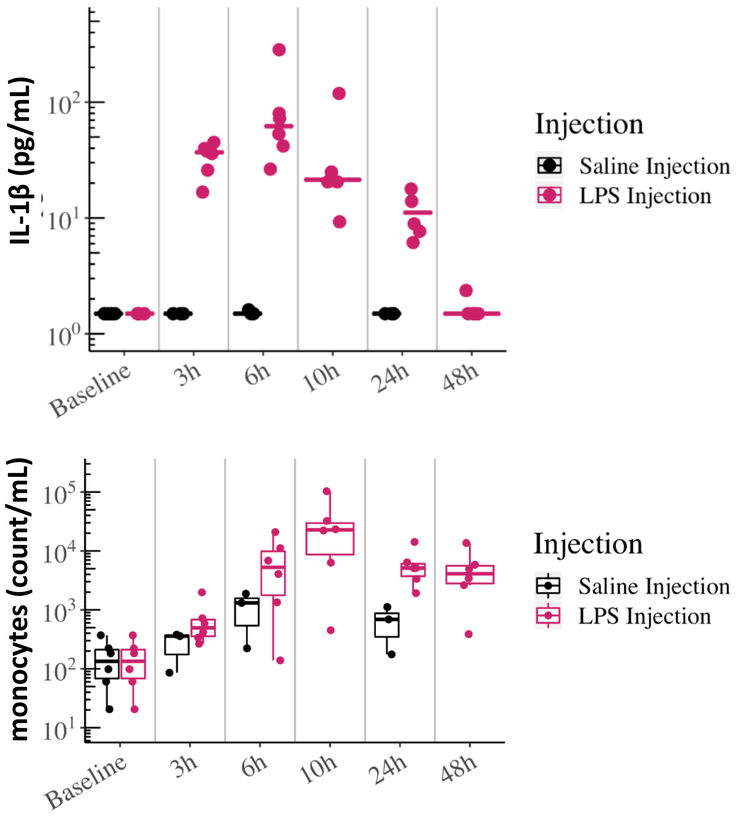

Figure 3: IL-1β production (top) and monocytes (bottom; HLADR+CD14+) after intradermal LPS challenge. X-axis: time after LPS administration.

Discussion

- LPS+ATP induces significant IL-1β and IL-18 production in fresh human whole blood cultures;
- Intravenously administered LPS induces a limited systemic IL-1β, but no IL-18 response;
- Intradermally administered LPS drives a robust local IL-1β response and enhances cellular influx;
- Conclusion: the *ex vivo* LPS+ATP challenge and the *in vivo* intradermal LPS challenge may be valuable models for future clinical trials investigating the effects of inflammasome/caspase inhibitors.

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