Ketamine as a modulator of LPS-induced innate immune response in mice

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Introduction

Lipopolysaccharide (LPS) induces a range of pleiotropic responses, which can be categorized into 'defense' or 'dormancy' programs. The defense program is marked by immune cell activation and anabolic metabolism. Simultaneously, dormancy programs—such as hypothermia, reduced metabolic rate, and catabolic metabolism—are activated, potentially supporting tissue protection.[1] Recent research has demonstrated that brainstem neurons, particularly in the NTS-AP region, are both necessary and sufficient for initiating dormancy responses following LPS injection.[2] Additionally, chemogenetic activation of specific vagal or cNST neurons modulated the cytokine response to LPS, altering the overall outcome.[3]

Previous studies have demonstrated that anesthetic agents can modulate cytokine levels in inflammatory conditions; however, their overall impact on outcomes remains unclear.

Research Question

Can anesthetic agents alter the body response to LPS and change its outcomes?

Methods

Mice
Male C57BL/6J mice, aged 8 to 10 weeks, were used for all experiments. Mice were intraperitoneally injected with a lethal dose (LD100) of LPS to induce endotoxemia. Ketamine (60 mg/kg) was administered intraperitoneally three times: 15 minutes before the LPS injection, 45 minutes after the LPS injection, and 165 minutes following the LPS injection.

Metabolic cage
Metabolic measurements were conducted using Promethion metabolic cages.

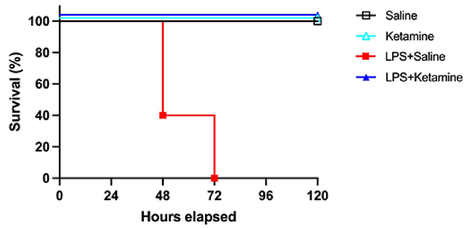
Cytokine measurements
Blood serum was collected via the intra-orbital route. Samples were analyzed using a multiplex assay on the Luminex platform.

iDISCO whole brain clearing and imaging
Mice were transcardially perfused with PBS, followed by 4% PFA. The brains were post-fixed for 24 hours, and then immunolabeling and whole brain clearing were performed. For imaging, cleared samples were acquired in a sagittal orientation using a light-sheet microscope. All analyses for whole-brain studies were conducted using ClearMap software.

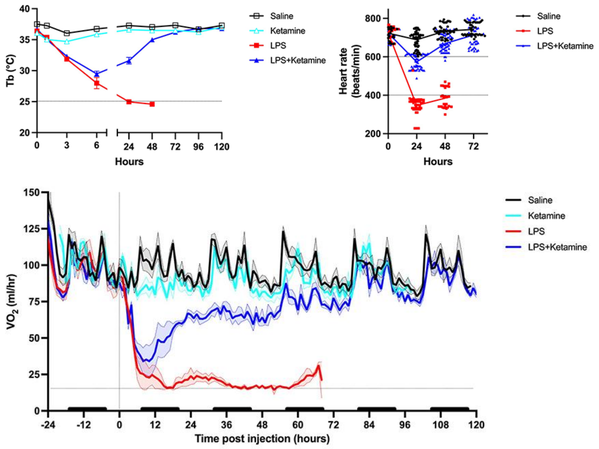
Results

1. Ketamine significantly improves LPS-induced lethality

Ketamine injection within the first 3 hours after LPS injection rescued mice from mortality. The LPS+Ketamine group exhibited a 100% survival rate compared to the LPS-only group.

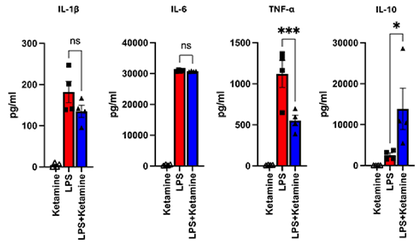


This improvement in survival was associated with rapid recovery in body temperature, heart rate, respiratory rate, pulse distention as well as metabolic rate.



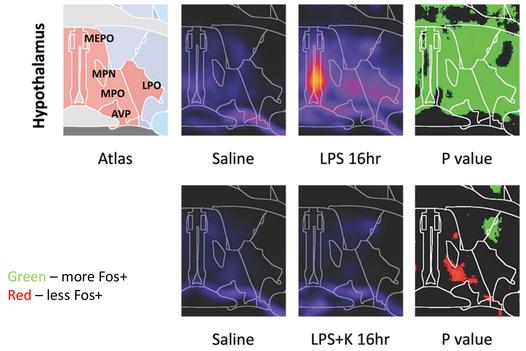
2. Ketamine modulates the cytokine response in vivo

In vivo ketamine injection resulted in a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokine levels. However, in vitro treatment of bone marrow-derived macrophages (BMDMs) with ketamine did not affect the mRNA levels of individual cytokines, suggesting that ketamine's effects on immune cells are likely indirect.



3. Ketamine suppresses LPS-induced activation of hypothalamic nuclei related to dormancy

The difference in brain activity aligned with the phenotypic and hemodynamic data, which showed that while the LPS-only group entered a steep torpid state following lethal-dose LPS, the LPS+Ketamine group recovered and returned to baseline conditions.



Conclusion

Ketamine mitigates LPS-induced prolonged hypometabolism, a potentially detrimental condition, thereby providing a survival advantage.

References

1. An evolutionary perspective on immunometabolism, Science 363 (Issue 6423), p. eaar3932, 2019
2. Brainstem ADCYAP1+ neurons control multiple aspects of sickness behaviour, Nature 609, 761-771, 2022
3. A body-brain circuit that regulates body inflammatory responses, Nature 630, 695-703, 2024