Lipopolysaccharide (LPS) administration by intraperitoneal (i.p.) injection induces neuroinflammation and anhedonia-like behaviour in rodents

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Introduction

Neuroinflammation has been linked to the pathogenesis and treatment of psychiatric disorders, including major depressive disorder (MDD)1. Anhedonia is a core symptom of psychiatric disorders and people with MDD commonly show motivational impairments. Tasks measuring effort-based functions have been suggested as models for such motivational symptoms. LPS is a component of the outer membrane gram-negative bacteria and has been shown to induce inflammation and behavioural changes in mammals.

Aims:
I) To assess the effect of systemic LPS administration on peripheral and central nervous system (CNS) inflammation in mice

II) To assess the effect of systemic LPS administration on motivation in rats

Methods: Experiment 1

- Male C57BL/6J mice (n=10 per group) received an i.p. injection of saline or LPS (0.25mg/kg)
- Plasma and brain (left hemisphere) were collected 4hr after LPS administration and cytokines (TNF-α, IL-6, IL-1β) were analysed using Meso Scale Discovery platform

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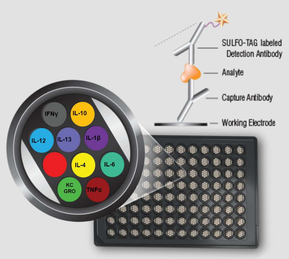

Methods: Experiment 2

- Male Sprague Dawley rats (n=10 per group) received an i.p. injection of saline or LPS (0.25mg/kg)
- Motivation was assessed in the progressive ratio (PR) task at 2, 24 and 48 hr after administration

Results: Experiment 1

Plasma cytokine concentration – 4hr post-LPS

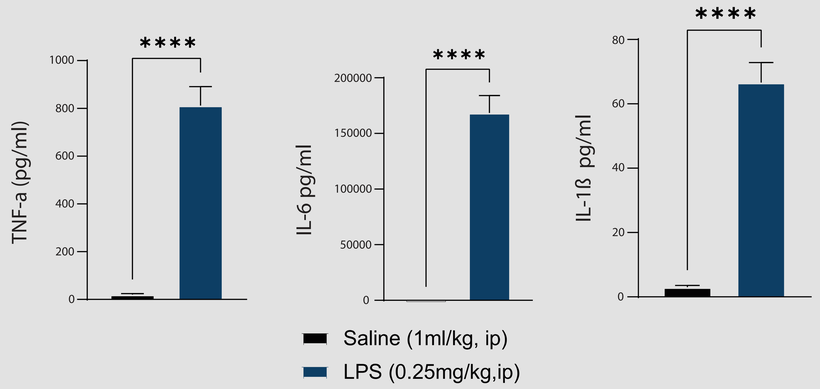

Figure 1
TNF-α, IL-6, IL-1β concentration in plasma
****p<0.0001, Student's t-test.

Mean ± SEM, n=4-10 per group

Brain cytokine concentration – 4hr post-LPS

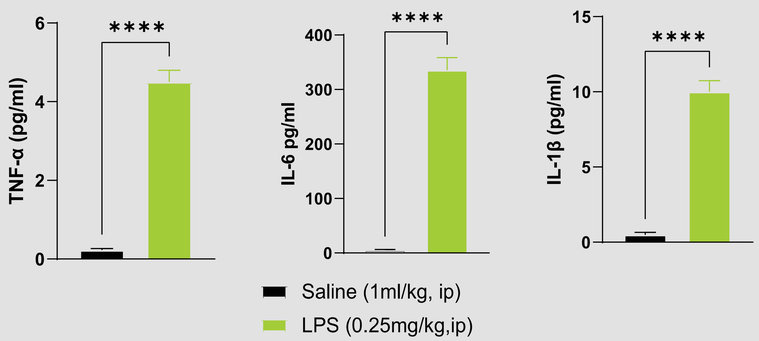

Figure 2
TNF-α, IL-6, IL-1β concentration in brain
****p<0.0001, Student's t-test.

Mean ± SEM, n=4-10 per group

Results: Experiment 2

Motivation in the PR task

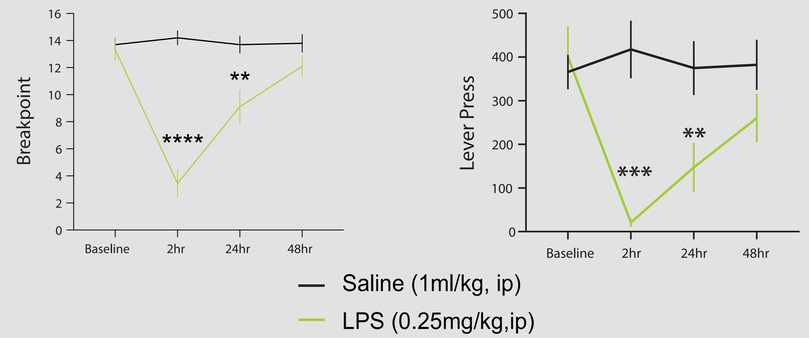

Figure 3
Breakpoint and lever press in the PR task **p<0.01, ***p<0.001, ****p<0.0001 vs. baseline, One-Way repeated measures ANOVA followed by Fisher's LSD.

Mean ± SEM, n=9-10 per group

Conclusion

The establishment of preclinical models of neuroinflammation-induced behavioural changes representative of depressive symptomatology is required to advance drug development. System administration of LPS administration in mice induced a robust inflammatory response in plasma and the brain. In rats, LPS induced a deficit in motivation in the PR task during the acute 'sickness behaviour period' (2hr after administration).

Motivational deficits were also observed at 24hr, a time point previously shown to be optimal for assessing depressive-like behaviour in rodents following inflammatory stimuli[2]. These data suggest that peripheral administration of LPS can be used to model neuroinflammation and anhedonia-like behavioural changes of relevance to MDD.

References

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[2] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008 Jan;9(1):46-56. doi: 10.1038/nrn2297. PMID: 18073775; PMCID: PMC2919277.

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