β-Funaltrexamine protects against lipopolysaccharide-induced neuroinflammation and behavioral impairment

OKLAHOMA STATE UNIVERSITY
CENTER FOR HEALTH SCIENCES

Stephanie Myers; Daniel J. Buck; Kelly McCracken; J. Thomas Curtis; Randall L. Davis

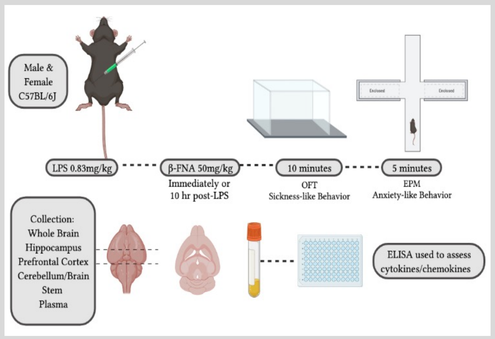
Contact: stephanie.myers10@okstate.edu

Department of Pharmacology/Physiology

Background

One of the commonalities present in a multitude of neurological disorders is inflammation. For this reason, targeting inflammation has emerged as a viable option for the potential treatment of neurological disorders. Previous work indicated that beta-funaltrexamine (β-FNA), a selective mu-opioid receptor (MOR) antagonist, not only inhibited inflammatory signaling *in vitro* in human astroglial cells but also inhibited lipopolysaccharide (LPS)-induced neuroinflammation and sickness-like behavior in male mice when administered immediately post-LPS. The present study explores the extent that β-FNA is protective when treatment occurs 10h after LPS administration and assess its protective effects at 24 h after treatment. It will also assess the effects of β-FNA on female mice, which to our knowledge has never been done before.

Methodology



Male and female C57BL/6J mice were administered LPS(i.p.) followed by treatment with β-FNA(i.p.) immediately or 10 h post-LPS. Sickness-like behavior was assessed using a 10-min open-field test and anxiety-like behavior was assessed by a 5-min elevated plus-maze test. This was followed by the collection of the whole brain, hippocampus, prefrontal cortex, cerebellum/brain stem, and plasma. Levels of inflammatory chemokines/cytokines (interferon γ-induced protein, CXCL10; monocyte chemotactic protein 1, CCL2; interleukin-6, IL-6; interleukin-1β, IL-1β, and Tumor Necrosis Factor Alpha, TNF-α) in tissues were measured using an enzyme-linked immunosorbent assay.

Results

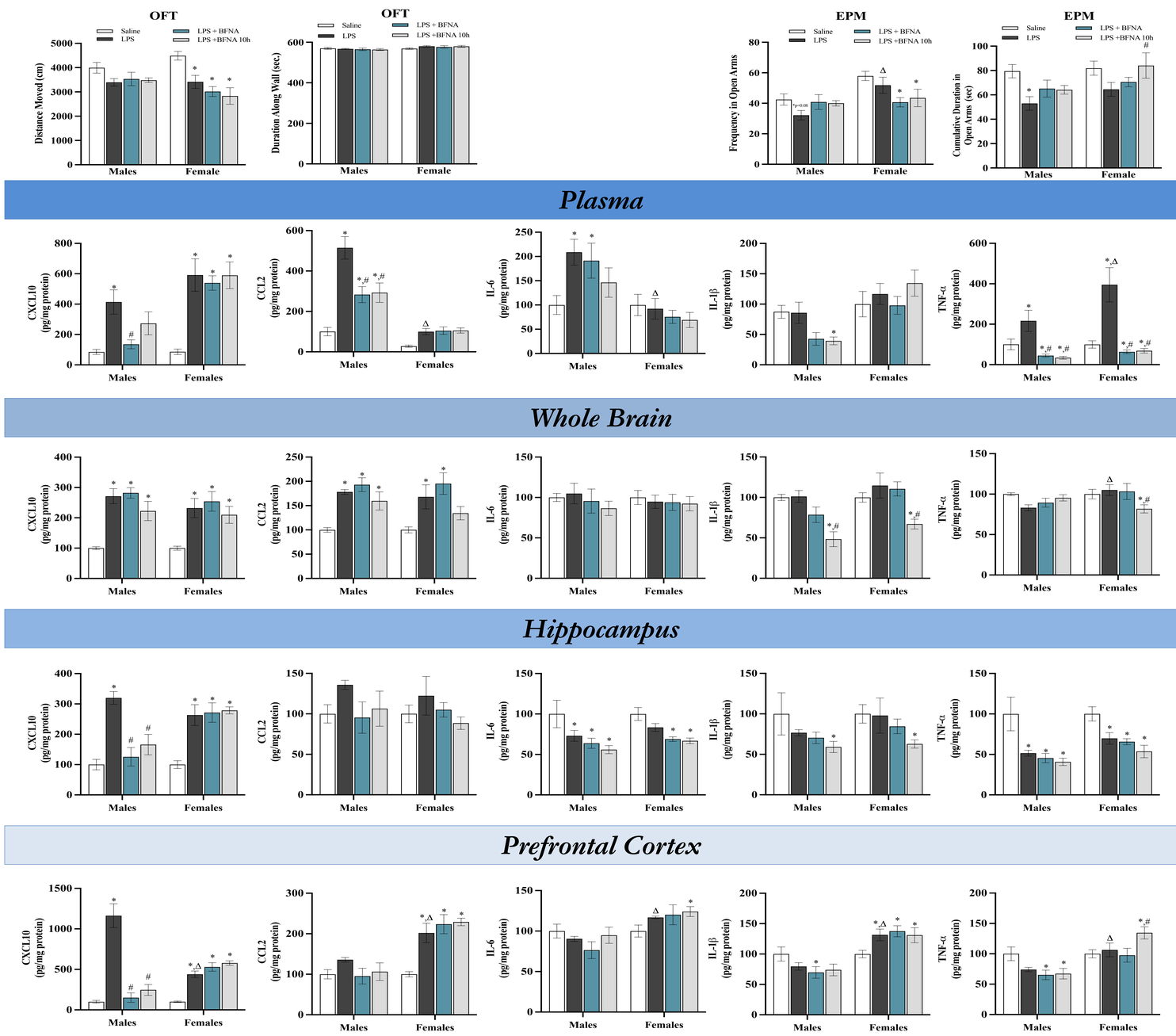


Fig 1. Effect of β-FNA on LPS-induced sickness and anxiety-like behavior and chemokine/cytokine expression. Mice were administered LPS (0.83 mg/kg; i.p.) followed by β-FNA treatment (50 mg/kg; i.p.) immediately or 10 h post-LPS injection. A 10-min. open-field test followed by a 5-min. elevated plus-maze test was performed 24 h after LPS administration, followed by tissue collection. CXCL10, CCL2, IL-6, IL-1β, and TNF-α levels in whole brain homogenates, hippocampus, prefrontal cortex, and plasma were measured by ELISA. Data reported as mean ± SEM (n=5-6) and analyzed by two-way ANOVA and Fisher's LSD. * $p < 0.05$ vs. saline group; # $p<0.05$ vs. LPS group; Δ $p<0.05$ vs. males LPS.

Conclusions

-Mice showed evidence of sickness-like behavior and β-FNA was not protective at this specific time point. EPM is a more accurate measure used to assess anxiety-like behavior. The data suggest a trend towards some level of anxiety-like behavior. β-FNA appears to show some level of protection, however, not to the level of significance.

-β-FNA is protective against LPS-induced CXCL10 in males but not females. It is also protective peripherally, but not in the whole brain. However, β-FNA is protective in select brain regions.

-LPS-induced CCL2 was brought back to baseline in the periphery in males but not in females. No effects were detected in the brain.

-IL-6 showed peripheral elevation only in males and no β-FNA protection (except slightly at 10 h). However, in the whole brain levels of IL-6 were not elevated.

-At this specific time point IL-1β levels do not differ in response to LPS in the plasma or brain tissue, except for the prefrontal cortex in females where there was some elevation. β-FNA was not protective.

-TNF-α was robustly elevated in the periphery in both males and females, yet there was no change in the brain. The peripheral elevation was prevented by β-FNA.

-All together there are differential effects of LPS, β-FNA, and in inflammatory factor responses between whole brain vs. brain regions and peripheral vs. central tissue. Additionally, there were sex-effects observed.

Future Directions

-Further assess temporal effects of β-FNA on neuroimmune signaling.

-Examine the effects of β-FNA on LPS-induced inflammatory signaling in peripheral tissues (i.e., spleen, liver, and intestines).

References

Davis, R. L., Stevens, C. W., & Curtis, J. T. (2017). The opioid antagonist, β-funaltrexamine, inhibits lipopolysaccharide-induced neuroinflammation and reduces sickness behavior in mice. *Physiology & behavior*, *173*, 52-60.

Funding

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