

Effects of centrally administered etanercept on behaviour, histology and *Tnfa* expression in mice following a peripheral immune challenge

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Background: Peripheral cytokines affect central nervous system (CNS) function, triggering anxiety and cognitive decline. Although peripheral blockade of tumor necrosis factor (TNF- α) by etanercept, has been effective in alleviating rheumatoid arthritis, it is yet unknown whether central blockade of TNF- α is beneficial for immune-challenged CNS function. This study investigated effects of central etanercept administration post-peripheral immune challenge, on behaviour and histology.

Methods: 12-week-old C57BL/6 mice (n=40) were challenged with either LPS or saline, administered peripherally 24hr before being treated with etanercept or artificial CSF (aCSF), via intracerebroventricular injection. Mice underwent behavioural analyses for locomotion (open field test: OFT), memory (Y maze) and anxiety (elevated zero maze: EZM) 24hr post etanercept/aCSF treatment. Brain tissue was then collected to estimate number of hippocampal microglia and expression of *Tnfa*.

Results: Acute systemic challenge with LPS decreased weight in mice at 24hr, and impaired locomotor activity. LPS significantly increased anxiety-like behaviour (2-way ANOVA: Interaction: $P=0.096$; Saline/LPS challenge: $P=0.0006$, aCSF/etanercept treatment: $P=0.0008$), which was reversed by etanercept and significantly reduced cognition in the Y Maze (Interaction: $P=0.037$, Saline/LPS challenge: $P=0.31$, aCSF/etanercept treatment: $P=0.80$), which was not reversed by etanercept. LPS challenge also increased *Tnfa* expression in the hippocampus (Interaction: $F_{(1,13)}=28.04$, $P=0.0001$, Saline/LPS challenge: $P=0.0003$, aCSF/etanercept treatment: $P=0.021$) and etanercept treatment was effective in reducing this *Tnfa* expression ($P=0.001$). Etanercept also significantly reduced microglial numbers within the hippocampus, which were increased following LPS administration (2-way ANOVA: Interaction: $P=0.0041$; Saline/LPS challenge: $P<0.0001$, etanercept/aCSF: $P=0.08$).

Conclusion: A single dose of etanercept was found to be effective in significantly decreasing anxiety, *Tnfa* expression and microglia numbers 48hr post-peripheral immune challenge. The present study suggests that there is effective cross-talk between peripheral and central immune systems. Additionally behavioural and biological changes caused by LPS challenge which may be mediated by TNF- α related central inflammation, were reversed by etanercept treatment.