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Systemic Or Central Inhibition Of Fatty Acid Amide Hydrolase Attenuates The Expression Of Inflammatory Mediators In Discrete Brain Regions Following Systemic Immune Challenge

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Neuroinflammation is a key component underlying several neurological diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis and psychiatric disorders including depression. Enhanced endocannabinoid tone *in vivo* has been shown to exert immunomodulatory effects both centrally and peripherally[1, 2]. However, there has been a paucity of studies examining the extent to which the brain's endocannabinoid system modulates neuroinflammatory responses. The present study examined the effects of inhibiting fatty acid amide hydrolase (FAAH), the enzyme primarily responsible for the metabolism of anandamide, both systemically and centrally, on endocannabinoid levels and cytokine expression in discrete rat brain regions following a systemic immune challenge.

Male Sprague Dawley rats (250-300g; n = 8-11) received PF3845 (10mg/kg i.p in ethanol:cremophor:saline 1:1:18, or 500nmoles, i.c.v in 100% DMSO), a selective FAAH inhibitor, or vehicle, 15 (i.c.v.) or 30 (i.p.) minutes prior to systemic administration of the bacterial endotoxin lipopolysacchardie (LPS) (100µg/kg, i.p.) . Animals were sacrificed 2 hours post LPS challenge, the hippocampus and frontal cortex dissected out, snap-frozen and stored at -80°C until assayed for cytokine expression and endocannabinoid concentration. The expression of various inflammatory mediators, including tumor necrosis factor (TNF)α, interleukin (IL)-1β, IL-6, IL-10 and IL-1ra, IκBα and suppressor of cytokine signalling 3 (SOCS3) were determined using quantitative RT-PCR. Concentrations of the endocannabinoids, AEA and 2-arachidonylglycerol (2-AG), and the related fatty acid ethanolamines, N-oleoylethanolamine (OEA) and N-palmitoylethanolamine (PEA), were determined using LC-MS-MS. Data were analysed using unpaired two-tailed t-test and $P < 0.05$ was deemed significant. Data below are presented as fold change from vehicle-treated control.

Anandamide, OEA and PEA levels in the frontal cortex were significantly increased following systemic (4.2, 10.8 and 14.9 fold, respectively) and i.c.v. (3.9, 7.5 and 9.3 fold, respectively) administration of PF3845 when compared to vehicle-treated counterparts. Similarly, in the hippocampus, OEA and PEA levels were significantly increased following systemic (3.8 and 4.4 fold, respectively) and anandamide, OEA and PEA were elevated following i.c.v. (4.3, 6 and 5.9 fold, respectively) administration of PF3845. Systemic administration of PF3845 significantly attenuated LPS-induced increases in IL-1β (2.6 fold decrease), TNFα (2.5 fold), IL-6 (2.3 fold), IL-10 (2 fold), IκBα (1.4 fold) and SOCS3 (1.6 fold) expression, in the frontal cortex, and IL-1β (3.2 fold), TNFα (2.4 fold), IL-6 (2.5 fold) and SOCS3 (1.6 fold), expression in the hippocampus, when compared to vehicle-treated counterparts. Central administration of PF3845 (i.c.v.) resulted in a significant decrease in TNFα (3.3 fold), IL-6 (5.8 fold), IL-10 (3 fold) and SOSC3 (2.6 fold) expression in the frontal cortex, and IL-1β (3 fold) and IL-10 (3.8 fold) expression in the hippocampus following LPS administration, when compared to vehicle-treated counterparts.

In conclusion, the present study demonstrates that both systemic and central administration of the FAAH inhibitor PF3845 attenuates LPS-induced cytokine expression in discrete brain regions, thus further supporting an important role for FAAH substrates in the brain in regulation of acute neuroinflammaotry responses.

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References

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