Further investigation on the immunomodulatory and anti-inflammatory effects of NeuroRestore ACD856, a Trk-PAM in clinical development for the treatment of Alzheimer's disease

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Background

BDNF and NGF, acting through Trk receptors, mediate neuronal survival, plasticity, and cognition in neurological disorders like Alzheimer's Disease (AD). NeuroRestore ACD856, a positive allosteric modulator of Trk receptors, passed phase-I trials with good safety, pharmacokinetics, and signs of CNS target engagement. In vivo, ACD856 increases BDNF, improves cognition and has long-term antidepressant effects. In vitro, it enhances neurite outgrowth, protects against Aβ toxicity and improves mitochondrial function. Recent findings showed that ACD856 decreases brain levels of IL-6, IL-1b and plasma IgG in aged mice and APP^{NLGF} knock-in mice models, offering a promising strategy to slow neurodegeneration in AD and other diseases characterized by a neuroinflammatory component.

Aim

The aim was to investigate the immunomodulatory effects of BDNF and ACD856 in a LPS-induced model of neuroinflammation using a microglia cell line.

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ACD856 mitigates LPS-induced levels of pro-inflammatory mediators in microglia.

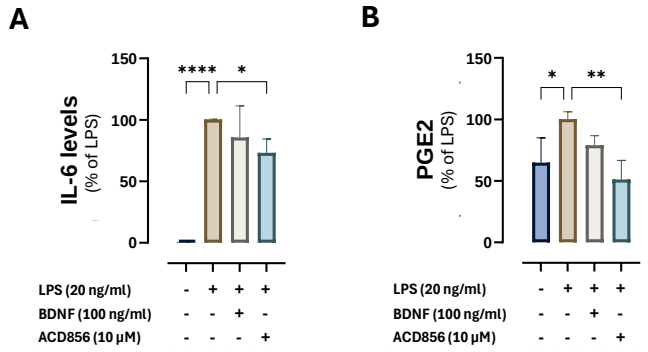
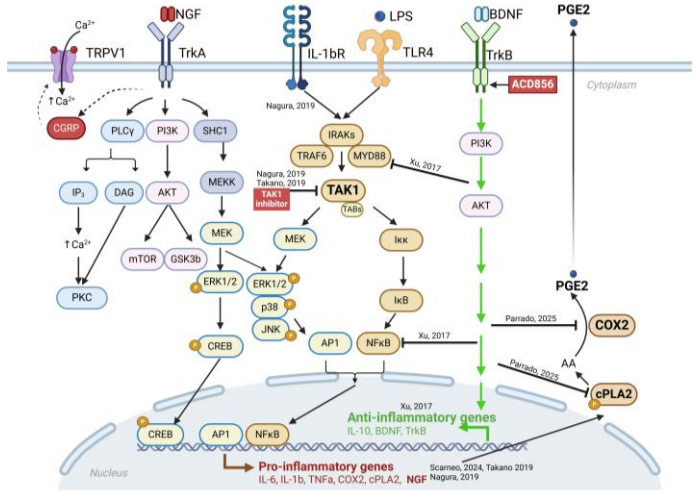


*Figure 2. Levels of IL-6 **(A)** and PGE2 **(B)** in conditioned media. Data are presented in percentage of LPS(+)PMA(+) group ± S.D, n=5 and n=2 experiments, respectively. Significant differences were determined by one-way ANOVA, followed by Tukey's multiple comparisons test. *p < 0.05, **p < 0.01, ****p < 0.0001 versus LPS(+)PMA(+) group.*

Anti-inflammatory actions of Trk signaling.



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ACD856 reduces the expression of COX2 and the phosphorylation of cPLA2 in BV2 microglial cells.

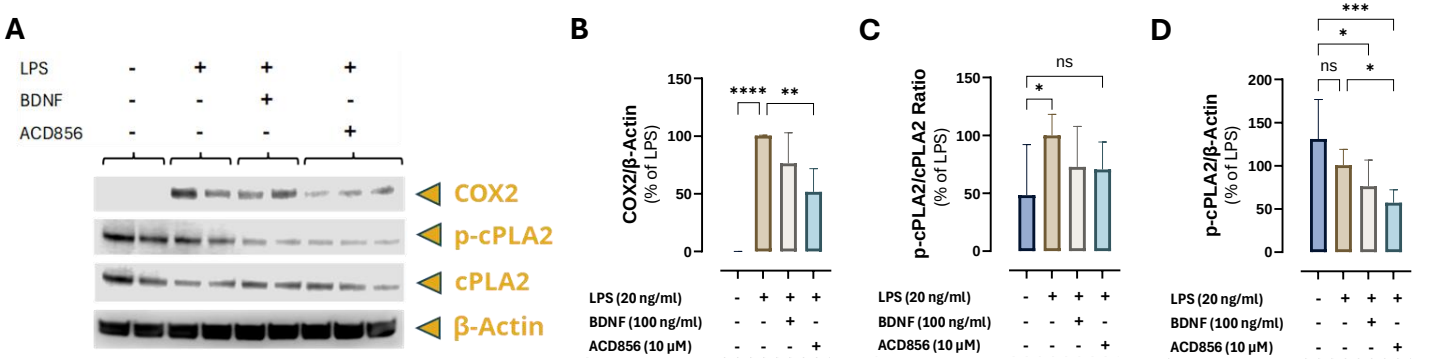

*Figure 3. Representative western blot images (A) and summary data (B, C, D) of protein expression levels of COX2 (n = 4), phospho-cPLA2 (n=3) and p-cPLA2/cPLA2 density ratio (n = 3) in the BV2 microglial cells. Data are presented in percentage of LPS(+)PMA(+) group ± S.D. Significant differences were determined by one-way ANOVA, followed by Tukey's multiple comparisons test. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 versus LPS(+)PMA(+) or LPS(-)PMA(+) groups.*

Methods

Microglial BV2 cells (Cytion, 305156) were stimulated 6 days with 10 ng/ml PMA, pre-treated with ACD856 or BDNF for 3h. Thereafter, LPS was added for 21h. Conditioned media was analyzed for IL-6 and PGE2 levels. Cell lysates were used to measure COX2, phosphorylated and total cPLA2 levels by western blot.

Results

Treatment of microglia cells with ACD856 led to reduced levels of LPS-induced soluble markers of inflammaton such as IL-6 and PGE2. Furthermore, ACD856 downregulated the expression of COX2 and the phosphorylated cPLA2 form by 50% in LPS-treated cells, correlating with the decreased release of PGE2 in the conditioned media.

Conclusion

Consistent with the reported anti-inflammatory effects of ACD856 in the brain of aging and APP^{NLGF} knock-in mice, we show that ACD856 is effective at downregulating IL-6, PGE2, COX2 and the phosphorylated cPLA2 form.

These findings suggest that ACD856 alongside its cognitive-enhancing and disease-modifying effects, may mitigate the activation of the neuroinflammatory response, a critical factor in the progression of AD, and therefore, slowing down neurodegeneration.

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