Chronic JZL184 treatment normalizes impaired striatal synaptic plasticity and motor learning in YAC128 Huntington disease mice

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Introduction

- In the genetic neurodegenerative disorder Huntington disease (HD), striatal degeneration is preceded by synaptic and circuit-level dysfunction
- Alterations in the expression and signaling of the CB1 cannabinoid receptor, a key component of the endocannabinoid (eCB) system, are observed in HD patients and mouse models
- Work from our lab has found that eCB-mediated long-term depression (LTD) is impaired in brain slices collected from YAC128 HD mice
- LTD can be rescued in YAC128 brain slices by JZL184 treatment

Methodology

- To assess the translational potential of targeting the eCB system in vivo, we chronically treated 5-month-old YAC128 HD mice with JZL184 for 20-25 days
- JZL184 was dissolved in peanut butter and administered orally to mice every day at a dose of 4 mg/kg
- Behavioural testing, including the accelerating rotarod and forced swim test, was performed from day 14 to day 20
- Following this treatment period, brain slices were collected for acute slice electrophysiology experiments
- Striatal tissue was also collected for mass spectrometry analysis of the endocannabinoids 2-AG and anandamide (AEA)

Chronic JZL184 treatment elevates 2-AG levels without affecting AEA

- Chronic JZL184 treatment resulted in a five-fold increase in the concentrations of 2-AG in the striatum (tissue collected within 4 hours of last dose)
- AEA levels were unaffected by JZL184 treatment

Motor impairments in YAC128 mice are no longer observed following JZL184 treatment

- Motor coordination was assessed using the accelerating rotarod test, with each mouse performing three trials per day over four days
- Control YAC128 mice had significantly impaired learning of the rotarod task as compared to WT mice
- Following JZL184 treatment, rotarod learning was not significantly different between WT and YAC128 mice
- Immobility time on the forced swim test, indicative of ‘depressive’-like behaviour, was significantly greater in YAC128 as compared to WT mice, and was increased in both genotypes following JZL184 treatment

Conclusions

- Chronic oral JZL184 treatment was effective at reversing neuroplasticity deficits in the YAC128 mouse model of Huntington disease, and modestly improved motor deficits in these animals
- These results provide evidence that targeting impairments in endocannabinoid signaling may be an effective strategy for recovering neuroplasticity and treating the early motor symptoms of HD