Chronic pharmacological inhibition of metabotropic glutamate receptors 5 (mGluR5) mitigates motor and cognitive impairments in a Huntington's disease mouse model

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Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that causes progressive motor and cognitive impairments. A mutant form of huntingtin protein characterized by an expanded polyglutamine repeats and ability to form aggregates is known to be the underlying cause of HD (1). Despite the well-characterized etiology and ability of early genetic diagnosis, to date there is no disease modifying drug for HD patients. Evidence suggests that alterations in metabotropic glutamate receptor 5 (mGluR5) signaling contribute to the progression of excitotoxic damage associated with HD. Moreover, genetic deletion of mGluR5 ameliorated motor dysfunction and mutant huntingtin-dependent pathology in Q111 knock-in HD mouse model (2). Here, we tested whether the acute and/or chronic blockage of mGluR5 using the orally bioavailable, selective negative allosteric modulator CTEP (2-chloro-4-[2-[2,5-dimethyl-1-[4-(trifluoromethoxy)phenyl]imidazol-4-yl]ethynyl]pyridine) will improve motor and cognitive deficits in Q175 knock-in mouse model of HD.

Method

Twelve month-old wild type, heterozygous Q175 (Q175/-) and homozygous Q175 (Q175/Q175) mice were orally-treated with either vehicle or CTEP (2mg/Kg) every 48 hours for 12 weeks. All groups were assessed following 1 week (acute) and 12 weeks (chronic) of treatment for changes in grip strength, performance on accelerating rotarod, limb placement/coordination on ladder rung walking task, and recognition of novel object.

Results

Acute treatment with CTEP did not significantly mitigate motor function in Q175/- or Q175/Q175 but significantly improved recognition scores of novel object in Q175/- (recognition index (RI) 59.05±3.3% (CTEP) vs 46.7±7.8% (Veh); n=12; $p<0.05$). Chronic CTEP treatment caused a significant improvement in : i) grip strength (125.4±2.9 mN (CTEP) vs 109.5±2.5 mN (Veh) in Q175/- and 78.3±3.7 mN (CTEP) vs 56.5±2.4 mN (Veh) in Q175/Q175 ;n=12; $p<0.05$), ii) latency to fall from rotarod (44.6±5.5 sec (CTEP) vs 28.6±3.8 sec (Veh) in Q175/Q175; n=12; $p<0.05$), iii) recognition scores (RI, 70.4±9.3% (CTEP) vs 53.5±7.1% (Veh) in Q175/- and 71.4±4.1% (CTEP) vs 55.7±7.4% (Veh) in Q175/Q175; n=12; $p<0.05$), and iv) %error in limb placement on ladder walking task in Q175/Q175. This was paralleled by CTEP-induced activation of autophagy markers and clearance of huntingtin aggregates from cortical and hippocampal brain regions.

Conclusions

CTEP improves cognitive and motor dysfunction and decreases the accumulation of mutant huntingtin aggregates in Q175 knock-in mice. Our findings indicate that CTEP is a viable drug target that could be repurposed clinically to rectify HD progression.

References

1.Ribeiro FM et al. (2014)**.** Expert Opin Ther Targets. **18**:1293-1304

2.Ribeiro FM et al. (2014). Hum Mol Genet. **23**:2030-2042