Cognitive deficits in Huntington’s Disease and altered 24(S)-hydroxycholesterol

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Introduction

- Nearly 25% of total body cholesterol resides in the central nervous system (CNS), where it is the principal component of myelin.1
- Lack of blood brain barrier permeability requires the conversion of cholesterol to 24(S)-hydroxycholesterol (HC) by the brain specific enzyme CYP46A1.2,3
- 24(S)-HC is a potent endogenous positive allosteric modulator (PAM) of the N-methyl-D-aspartate (NMDA) receptor.4

Conclusions

- Our data support a role for 24(S)-HC in cognitive processes in HD and suggest that NMDA hypofunction may contribute to cognitive impairment in HD.
- The associations do not appear to be driven solely by neurodegenerative processes, and the associations are specific to 24(S)-HC (No associations were observed with 25-HC or 27-HC; data not shown).
- SAGE-718, an investigational NMDA positive allosteric modulator, is currently in clinical development for HD (Phase 1).

Results

24(S)-HC ASSOCIATIONS ACROSS TRACK-HD

- 24(S)-HC correlations in years one, three, and four of TRACK-HD.
- Strong relationships between 24(S)-HC and cognitive measures were present across the years of TRACK-HD.
- Data are represented as –Log P value of regression P value.

EFFECT ON COGNITION: WORKING MEMORY AND PROBLEM SOLVING

- SAGE-718 significantly improved working memory at Days 2, 4 and 8, and executive functioning at Day 6 in a Phase 1, multiple ascending dose study in healthy volunteers.
- Those endpoints that were significantly correlated with oxysterol levels within year 2 were then tested against samples from years 1, 3, and 4 (hypothesis testing).
- A mixed model for repeated measures was applied, with change from baseline in each cognitive assessment test score as the response variable and treatment, visit by treatment interaction as fixed effect, baseline as covariate, and measurements within the same subject as interaction as fixed effect.