Stimulation of Sphingosine Kinase 1 (SPhK1) Is Beneficial in a Huntington’s Disease Pre-clinical Model

Alba Di Pardo, Giuseppe Pepe, Salvatore Castaldo, Federico Marracino, Luca Capocci, Enrico Amico, Michele Madonna, Susy Giove, Se Kyoe Jeong, Bo-Mahn Park, Byoung Deog Park, and Vittorio Magliore

Although several agents have been identified to provide therapeutic benefits in Huntington disease (HD), the number of conventionally used treatments remains limited and only symptomatic. Thus, it is plausible that the need to identify new therapeutic targets for the development of alternative and more effective treatments is becoming increasingly urgent. Recently, the sphingosine-1-phosphate (S1P) axis has been reported to be a valid potential novel molecular target for therapy development in HD. Modulation of aberrant metabolism of S1P in HD has been shown to exert neuroprotective action in vitro settings including human HD (R6/2) derived neurons. In this study, we investigated whether promoting S1P production by stimulating Sphingosine Kinase 1 (SphK1) by the selective activator KEPc-S, may have therapeutic benefit in vivo in R6/2 HD mouse model. Our findings indicate that chronic administration of 0.05 mg/kg KEPc-S exerted an overall beneficial effect in R6/2 mice. It significantly slowed down the progressive motor deficit associated with disease progression, modulated S1P metabolism, evoked the activation of pro-survival pathways and markedly reduced the toxic mutant huntingtin (mHtt) aggregation. These results suggest that KEPc-S may represent a future therapeutic action in HD and may potentially counteract the portended brain function induced by deregulated S1P pathways.

Keywords: HD, KEPc-S, SphK1, aggregates, neuroprotection

INTRODUCTION

Huntington’s disease (HD) is a fatal inherited brain disorder characterised by progressive striatal and cortico-spinal degeneration and associated motor, cognitive and behavioural disturbances (McGeehan and Taborin, 2017). The disease results from the expansion of a polyglutamine stretch (polyQ >36 repeats) in the N-terminal region of huntingtin (Htt), a widely expressed protein whose function is still under investigation (Jimenez-Sanchez et al., 2017).

Expansion of the polyQ tract endows mutant Htt (mHtt) with toxic properties, resulting in the development of a number of deleterious effects in both neuronal and non-neuronal cells (Magloire et al., 2005, 2006a,b; Carroll et al., 2015; Jimenez-Sanchez et al., 2017).
The dynamic process of developing theories in MEDICAL science
• Introduction to the TOPIC
• DISCUSSION of the hypothesis
• Experimental DESIGN
• ANALYSIS of experiments
• INTERPRETATION of data
• Preparation of FIGURES
• Discussion of RESULTS

Conclusion and debate!!!
Software required:

ImageJ
Excel
Photoshop
VLC media player
Analysis of experiments:
- animal behavioral tests
- molecular biology assay
- biochemical and histological experiments

Statistical analysis
Graphical representation of RESULTS & INTERPRETATION
CLASROOM DISCUSSION

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