Effect of Hfe deficiency on neurobehavioral toxicity after manganese exposure in drinking water

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BACKGROUND AND SIGNIFICANCE

- Hereditary hemochromatosis, an iron overload disorder, is one of the common genetic disorders in the Caucasian population.¹
- Mutations in HFE protein is the major cause of hemochromatosis.
- Up-regulated activity of intestinal iron transporters (divalent metal transporter 1 and ferroportin) is consistent with increased body iron status in hemochromatosis.²

Manganese (Mn) is an essential metal, but is neurotoxic in excess. Exposure to Mn is associated with abnormal brain function, including impaired motor function, memory deficits and psychiatric disorders.

Our previous experiment showed an increase in brain uptake of Mn after intranasal instillation in Hfe⁺/⁺ mice,¹ suggesting that loss of HFE function could modify manganese neurotoxicity.

Objective: To examine the role of Hfe in Mn-induced behavioral deficits.

METHODS

- Animals: Hfe knockout (Hfe⁻/⁻) and wild type (Hfe⁺/⁺) mice on the 129SV/SvTac background (n = 15-17 per group). Animal protocol (12-06159) was approved by the Northeastern University Animal Care and Use Committee.
- Mn exposure: Weanling mice were exposed to 5 mg/mL of MnCl₂ in drinking water ad libitum for 5 weeks.
- Analysis: All data were collected manually except for EPM, which was an EPM maze (Stoelting) used to count the time spent in open arm and track total distance traveled. Data were presented as means ± SEM. Groups were compared by two-way ANOVA followed by post-hoc analysis using SigmaPlot (Systat). P < 0.05 was considered significant difference.

Behavioral studies:

- Elevated plus maze (anxiety test)

The maze contains 20 false holes including only one escape hole. Each mouse was placed in the middle of the maze. Then footfalls were turned on to enforce mice to find the escape hole. Mice were trained to find the escape hole for three days with days of visual cues on the surrounding walls. On the fourth day, the escape hole was removed and replaced with the regular false hole that is similar to the red. The mice were tested to locate the target hole within 90 seconds by counting the latency to find the target hole.

RESULTS

- Mn exposure

Mn-exposed Hfe⁻/⁻ mice spent more time to find the escape hole on day 1 of training phase. However, all 4 groups showed improved learning ability to locate the escape hole on the second and third days.

CONCLUSIONS

- Hfe deficiency increased anxiety levels regardless Mn exposure.
- Mn exposure in drinking water decreased the spatial memory function in Hfe⁻/⁻, but not in wild-type mice.
- This result suggests a protective role of Hfe protein against Mn-induced memory deficits.

FUTURE STUDIES

- To further investigate for the toxic effect of Mn and Hfe deficiency on memory function, measurement of regional brain Mn levels, determination of neurotransmitters and oxidative stress biomarkers will help understanding the underlying mechanisms.

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References: