Effects of dietary enhancement of iron on Aβ and behavior in Wt2576 and Tg2576 mice.

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Introduction

Abnormally elevated levels of iron in the brain can be seen in several different neurodegenerative disorders, including Alzheimer's disease (AD) (Bishop et al., 2002). AD patients demonstrate more iron in the neuropil than patients who do not have AD (Lovell et al., 1998). Aβ protein has been discovered to have metal-ion binding sites and the direct interaction that occurs between APP and iron is a factor considered to be responsible for the aggregation and accumulation of Aβ (Huang et al., 2004). Accumulation of amyloid and changes in rates of iron metabolism appear to contribute to oxidative stress, which leads to neurodegeneration. The present study sought to examine the relationship between iron and Aβ through dietary enhancement in the drinking water.

Methods

Experiment 1:

Tg2576 (n=16) and Wt2576 (n=18) mice were raised pre- and post-natally on either lab water or lab water containing 10ppm iron nitrate ($Fe(NO_3)_2$). At 12 months of age, animals were tested in a MWM (using 2 different paradigms) to examine any deficits associated with iron consumption. The first paradigm consisted of a stationary platform with 3 trials a day and the platform submerged on every 6th trial (Atlantis). This was followed using a moving platform, that was in a different location each day, with four trials per day.

Experiment 2:

Tg2576 (n=30) and Wt2576 (n=31) mice were raised post-natally on either lab water, lab water containing 10ppm iron nitrate ($Fe(NO_3)_2$), or lab water containing 10ppm $ZnCO_3$ (zinc animals were included to confirm previous data and will not be further discussed here). At 12 months of age animals were tested in a MWM. In this paradigm the platform remained in the same place (in a different position than it had been for previous stationary trials) and was not lowered until a probe trial was run at the end. This consisted of 4 trials a day for 6 days.

Results

The data were analyzed using a repeated measures ANOVA, across all days, between water groups and genotypes. Experiment 1 data showed a significant effect over trials and between genotypes but no effects between water types ($F(1,30)=5.6$, $p<.05$) (Figures 1&2).

Experiment 2 data showed that there was a trend amongst Tg mice for a significant effect due to water type ($F(2,27)=3.2$, $p<.07$). Post-hoc tests showed that the Tg mice raised on zinc and iron had impaired spatial memory compared to those raised on lab water when days 4-6 were considered ($p<.05$). The mice raised on either zinc or iron did not improve over days or trials, whereas the lab Tg mice did (Figures 3-9).

*All graphs show latency to find the platform for Experiments 1 & 2, graphs for Experiment 2 show only Tg data.

Figures

Experiment 1

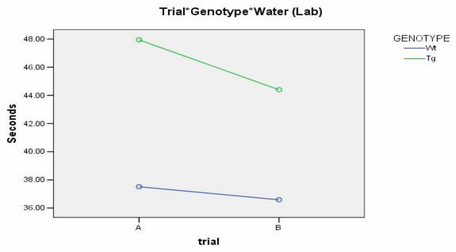

Fig 1.

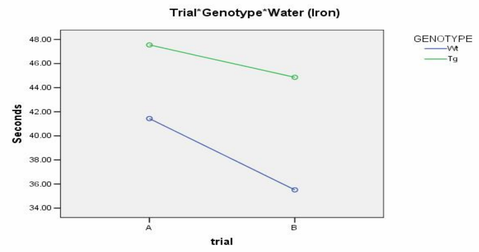

Fig 2.

Experiment 2

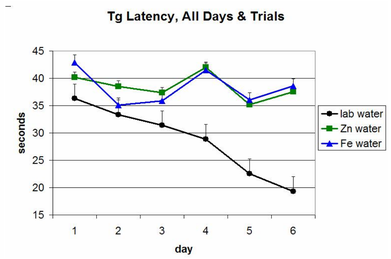

Fig 3.

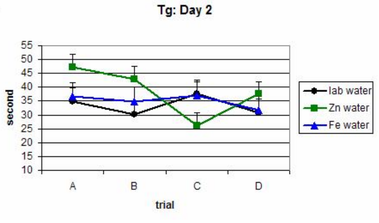

Fig 4.

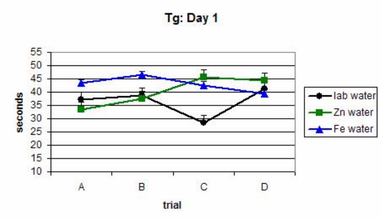

Fig 5.

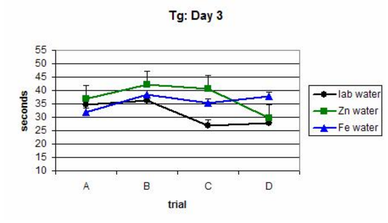

Fig 6.

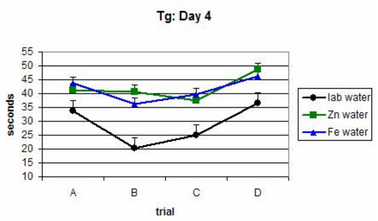

Fig 7.

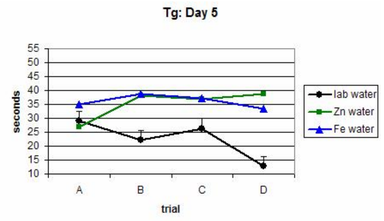

Fig 8.

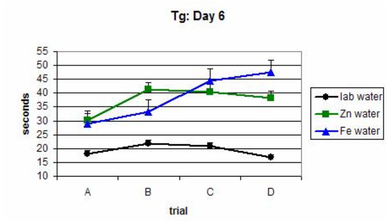

Fig 9.

Conclusions

Experiment 1 data showed an effect of genotype as expected, but did not demonstrate the predicted effect between water types. As a result, Experiment 2 was run using a different paradigm that demonstrates a greater test of spatial learning in Tg mice. The original test—the Atlantis paradigm—was modeled after a rat experiment. However, we found this to be a poor task for Tg2576 mice, as little or no learning seemed to occur. Although, surprisingly the strongest performers were Wt iron mice on B trials. Experiment 2 data showed there was a clear distinction between forgetting overnight (A trials) as opposed to forgetting between trials (B, C, & D). The A trials showed that all Tg animals forgot overnight, but those raised on lab water showed some learning, in contrast those raised on iron (and zinc) did not. These experiments suggest that Tg animals raised on iron seemed to have the greater deficits in spatial memory tasks.

References and Acknowledgements.

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