BEHAVIORAL ANALYSIS AND NEUROGENESIS IN MICE OVEREXPRESSING ERYTHROPOIETIN

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INTRODUCTION

Erythropoietin (Epo) is produced in the kidneys under hypoxic conditions to increase erythrocytes.

- Healthy volunteers, psychiatric patients and healthy mice have been treated with either an acute injection or a longer treatment of Epo showing positive effects on learning, memory, attention and mood.
- Healthy mice treated with Epo and its carbamylated derivative also increased neurogenesis in the dentate gyrus.
- The studies suggest that Epo could modulate plasticity, synaptic connectivity and activity on memory-related neuronal networks.

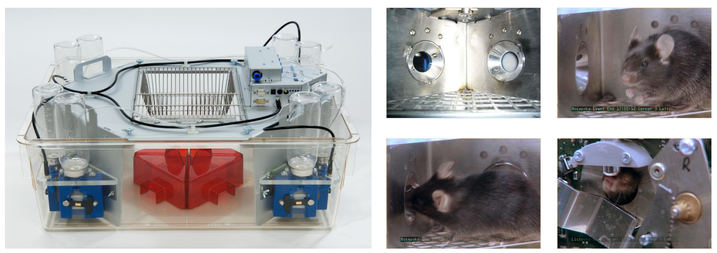
Aim of the study: to investigate the effect of the overexpression of endogenous Epo on learning, memory and neurogenesis.

METHODS

Two transgenic mouse lines: **Tg21** chronically overexpressing Epo in the brain (4-fold times more than a wild-type (Controls) without changes in blood parameters, and **Tg6** systemically overexpressing Epo (26-fold increased of Epo levels in the brain and 12-fold in plasma). A total number of sixty-five female animals were tested (Tg21, n=17; Control, n=16; Tg6, n=16; Control, n=16).

Behavioral tests: Morris Water Maze, 8-Radial Maze, T-Maze and Fear Conditioning.
Behavioral tests in the IntelliCage (www.newbehavior.com): Conditioned Nosepoke Suppression, Place Learning, Serial Reversion, Patrolling and Chaning.

The right hemisphere of the brain was cut in forty-um thick sagital sections. **Proliferating cells** were stained with Ki67, **differentiating cells** were stained with DCX and the **total number of granule cells** were visualized with a Giemsa staining. A total number of twenty-four female animals were tested (Tg21, n=6; and Control, n=6, 14 months old; Tg6, n=6, 6 months old; Control, n=6, 6.5 months old)



CONCLUSION

1. As opposed as acute models chronic overexpression of Epo did not have any effect on learning and memory in any of the behavioral tests performed.
2. We did not observe any changes in proliferating cells, differentiating cells or total number of grenule cells in the dentate gyrus of the hippocampus.
3. These results narow Epo's brain impact to the previous observations in reduced impulsitivy and increased anxiety.

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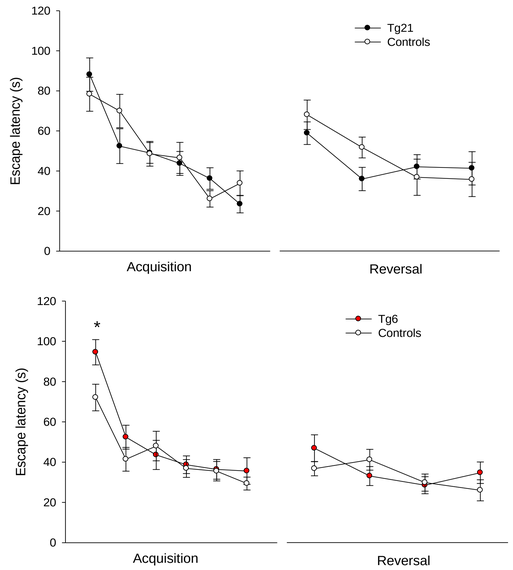
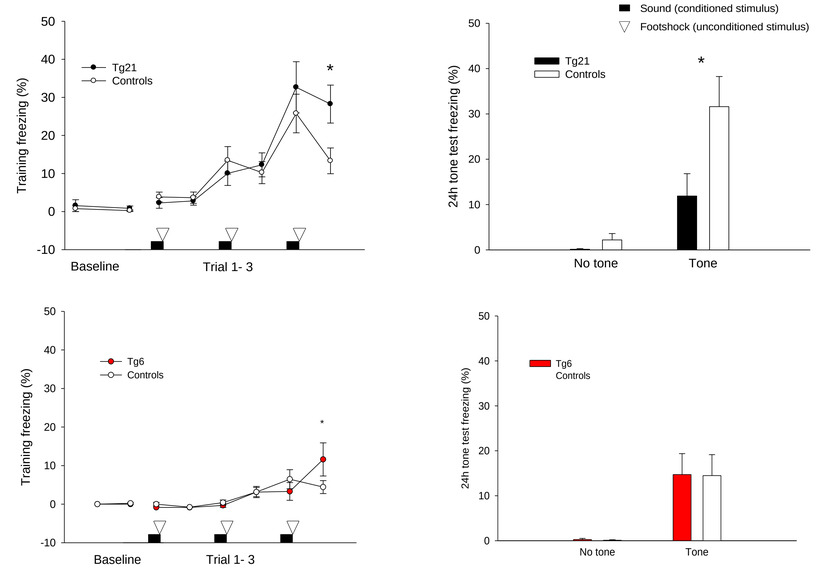
RESULTS

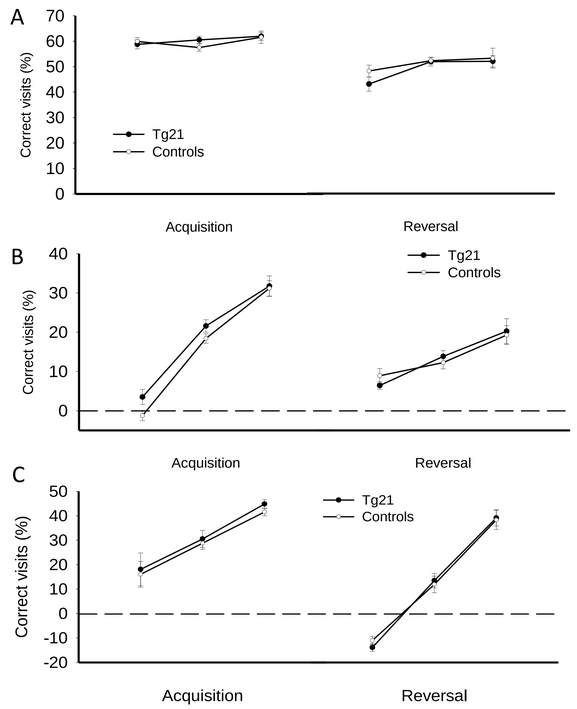
Morris Water Maze: Transgenic and control animals performed at a similar level during the Morris Water Maze test.



Fear Conditioning test: Despite the initial increased reaction of the transgenic animals after the third footshock, they showed a similar (Tg6) or lower (Tg21) memory performance 24h after the firs test.



IntelliCage protocols: During Serial Reversion (A), Patrolling (B) and Chaining (C) mice can drink from one correct corner that changes according to different patterns. In both, acquisiton and reversal phase control and transgenic animals showed a similar perfomnace level at learning and memory. Tg6 animals could not carry out these tests.



Neurogenesis: We found the expected differences between younger and older animals in proliferation and neuronal differentiation, but there was no difference between transgenic and control animals..