Spatial learning as activator of hippocampal neurogenesis during aging and development of Alzheimer's disease-like pathology

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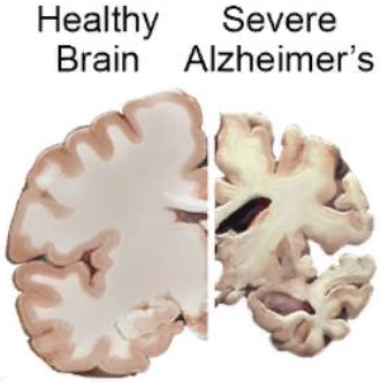
Abstract

Adult neurogenesis in dentate gyrus (DG) is one of the key mechanisms of neuronal plasticity in hippocampus and plays an important role in cognitive function. However, the consequences of its alteration during healthy aging as well as development of neurodegeneration including Alzheimer's disease (AD) remain unclear. It was shown that factors which can activate neurogenesis – such as physical exercises and learning – are able to improve cognitive function. Animal models are useful to clarify the connection between adult neurogenesis and cognitive function during development of AD signs, and OXYS rats are a suitable model for the most common sporadic form of AD. Here we examined effects of spatial learning on neurogenesis in DG of OXYS rats prior to and during manifestation of AD signs. We showed altered reference memory of OXYS rats already at the period prior to neurodegeneration (1.5 months). At the period of active manifestation of AD signs (3 months) OXYS rats demonstrated altered spatial learning and reversal learning, whereas reference memory was altered only a little. At the period of active amyloid-β accumulation (12 months) in the brain only reference memory of OXYS rats was altered. Spatial learning resulted in accelerated maturation of immature cells of neuronal and astrocytic cell lineages in DG of OXYS and Wistar rats (control) and decrease of amyloid-β content in aged animals.

Alzheimer's disease (AD) is detrimental multifactorial disorder developing asymptomatically for many years prior to its manifestation



https://www.nia.nih.gov

OXYS rats as a model of sporadic AD

http://pixie.bionet.nsc.ru

95% sporadic form

age of onset: >65 years

5% familial form

(mutations in *APP*, *PSEN1* and *PSEN2*);
age of onset: 30-60 years

1.5 months: absent of neurodegenerative changes

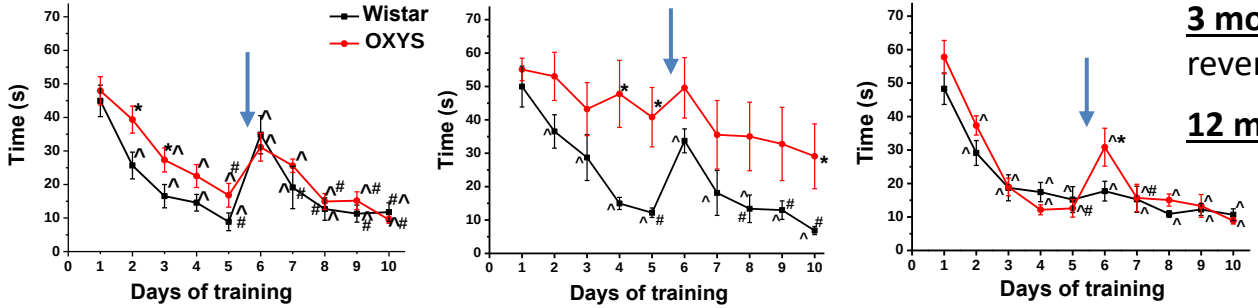
3 months: active manifestation of AD signs

12 months: active amyloid-β accumulation

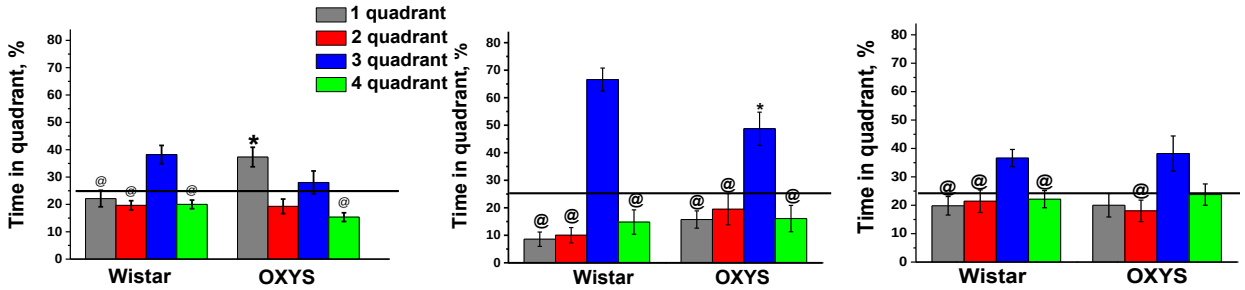
ALTERNATIONS OF SPATIAL LEARNING IN MORRIS WATER MAZE (MWM) OF OXYS RATS

1.5 months: **3 months**: **12 months**:

Escape latency (1st to 10th days of training)



Reference memory (11th day of training)



OXYS rats:

1.5 months: decrease of reference memory

3 months: altered spatial learning and reversal learning

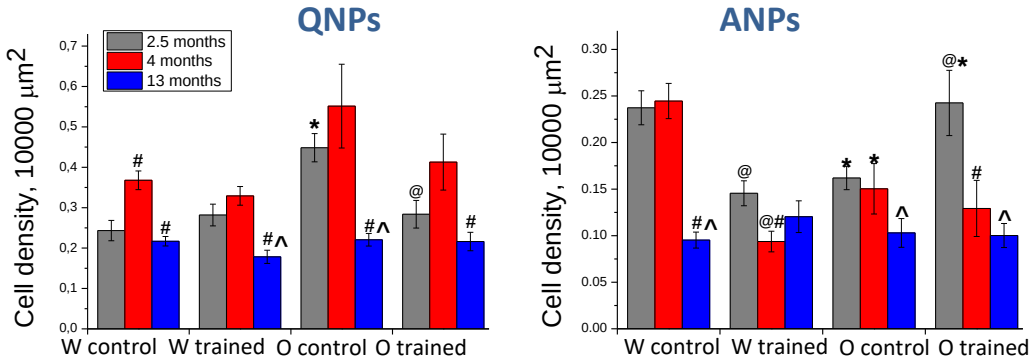
12 months: decrease of reference memory

Location of the platform:

1st-5th days – 1st quadrant
6th-10th days – 3rd quadrant
11th day – platform was removed

** p < 0.05 for differences between the strains; ^ p < 0.05 for comparison with the 1st day of testing; # p < 0.05 for comparison with the 6th day of testing; @ p < 0.05 for comparison with time in 3rd quadrant;* → - relocation of the platform to the 3rd quadrant

LEARNING IN MWM STIMULATED NEUROGENESIS IN THE DG OF OXYS AND WISTAR RATS

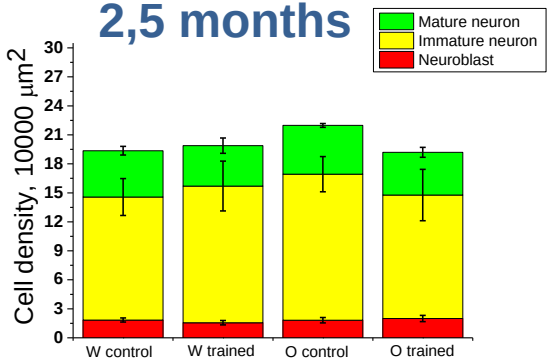


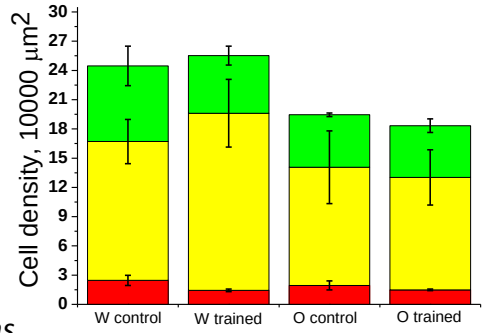
Learning in MWM:

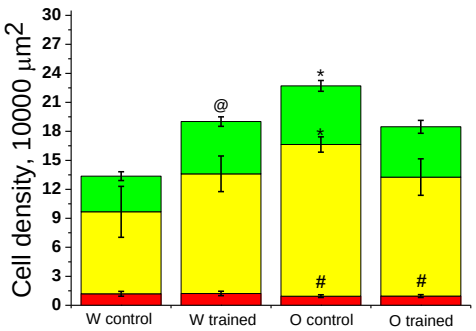
2.5 months: activation of QNPs resulted in increase of ANPs density in OXYS rats.

4 months: accelerated maturation of immature cells of neuronal lineage in Wistar rats.

13 months: the density of mature neurons increased in Wistar rats.







*$p < 0.05$ for differences between the strains

#$p < 0.05$ for differences with previous age

^$p < 0.05$ for differences with 2,5 month

@$p < 0.05$ for effects of MWM training

QNPs - quiescent neural progenitors

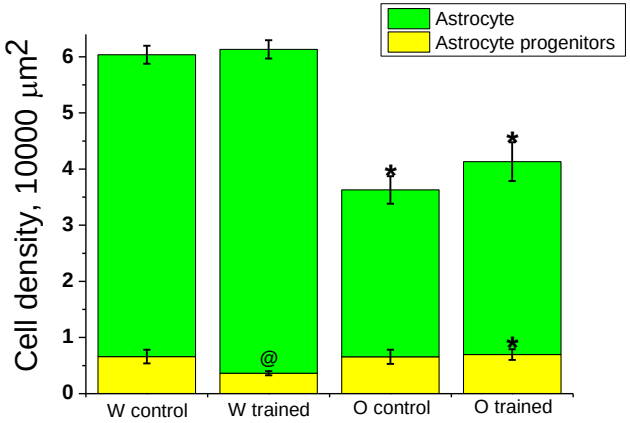
ANPs - amplifying neural progenitors

W - Wistar

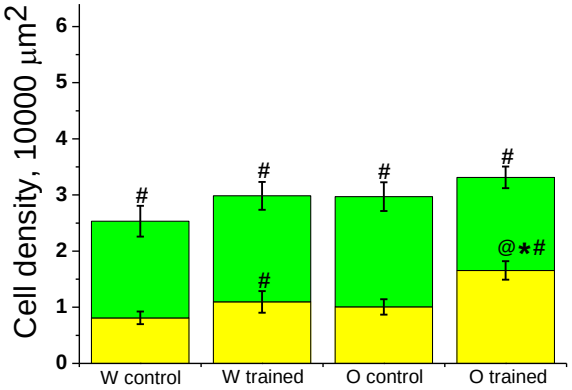
O - OXYS

LEARNING IN MWM ACTIVATED ASTROCYTOGENESIS IN THE DG OF OXYS AND WISTAR RATS

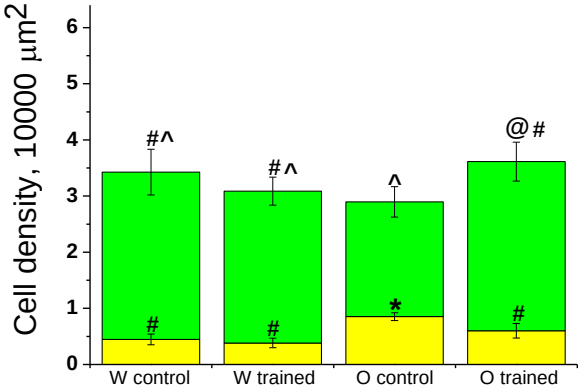
2,5 months



4 months



13 months



Learning in the MWM:

2.5 months: intensified maturation of astrocyte progenitors in Wistar rats

4 months: increase of astrocyte progenitors' density in OXYS rats

13 months: slight decrease of astrocyte progenitors' density and significant increase of astrocyte density indicating intensification of its maturation in OXYS rats.

**p < 0.05 for differences between the strains*

#p < 0.05 for differences with previous age

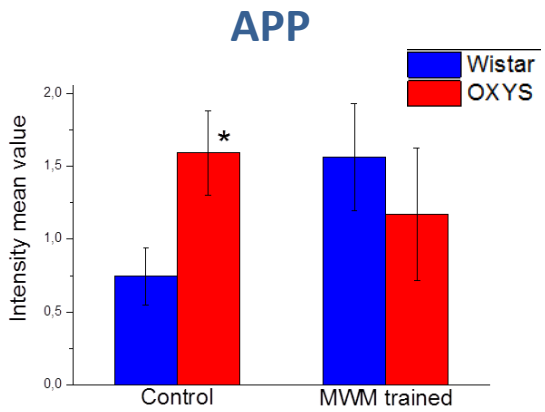
^p< 0.05 for differences with 2,5 month

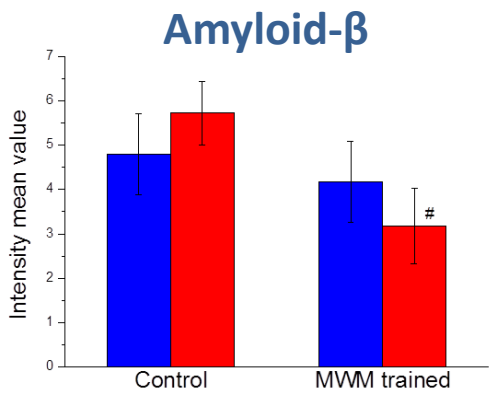
@p < 0.05 for differences with training

W - Wistar

O - OXYS

EFFECT OF SPATIAL LEARNING ON AMYLOID–β ACCUMULATION IN DG OF OXYS RATS





* p < 0.05 compared to Wistar rats

\# p < 0.05 compared to untrained animals

Training in MWM from 12 months of age decreased levels of amyloid-β in OXYS rats

APP – amyloid precursor protein

CONCLUSION

We demonstrated that spatial learning affected neurogenesis, however the impact depended on the age at which the animals were trained and the stage of AD-like pathology. Naturally, this positive effect was stronger for young adult rats and less clear when signs of AD in OXYS rats were already developed. Learning also lowered the content of amyloid-β in the DG of aged animals. Thus, hippocampal-dependent learning may be considered as a perspective strategy to intensify neuronal plasticity and thereby improve cognitive function even in aged animals and probably in elder people.

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MATERIALS AND METHODS

To evaluate spatial learning, reversal learning and reference memory of OXYS and control Wistar rats at 1.5, 3 and 12 months of age (n = 8 animals per strain and age) we used Morris water maze. To analyze changes in hippocampal neurogenesis of OXYS and Wistar rats we evaluated density of progenitors and cells from neuronal and astrocytic lineages (n = 3 to 6 per group, strain and age) in DG and the content of amyloid-β by immunohistochemistry using antibodies specific for molecular markers of various cell types as well as for amyloid-β.

RESULTS

Decrease of reference memory in OXYS rats was observed already at 1.5 months of age; however, spatial learning and reversal learning did not differ compared to Wistar rats. At the period of active manifestation of AD meaning 3 months of age OXYS rats demonstrated totally altered spatial learning and reversal learning, whereas reference memory was altered only a little. We observed decrease of reference memory in OXYS rats at stage of amyloid-β accumulation in the brain (12 months of age); however, we did not show any differences in learning and reversal learning abilities between OXYS and Wistar rats at this age. Learning in the Morris water maze from 1.5 months of age resulted in accelerated maturation of immature cells of neuronal and astrocytic cell lineages in Wistar rats and only immature cells of neuronal cell lineage in OXYS rats. Learning from 3 months of age accelerated maturation of immature cells of neuronal lineage in Wistar rats as well as activated astrocytogenesis in both OXYS and Wistar rats. Learning from 12 months of age did not affect cell densities in DG of Wistar rats and resulted in accelerated maturation of immature cells of astrocytic lineage in hippocampal neurogenic niche in OXYS rats. Learning from 12 months of age also affected amyloid-β content in DG: indeed, the parameter was lower in animals trained in Morris water maze.