Changes in Expression of Genes Associated with Neurogenesis during Development of Alzheimer's Disease Signs in OXYS Rats

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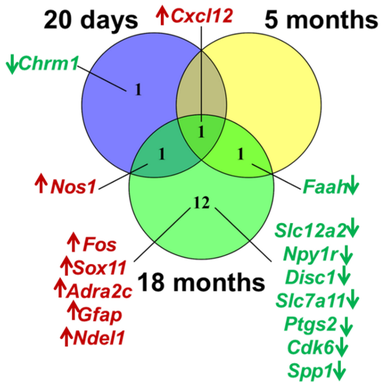
Motivation and Aim: Alzheimer's disease (AD) is the most common type of age-related dementia worldwide. However, the precise mechanisms of its pathogenesis are not fully understood. One of the processes that may contribute to neurodegeneration is alteration of neuronal plasticity. Neurogenesis is one of the major mechanisms of neuronal plasticity, and neurotrophic supply is crucial for it. Using OXYS rats as a suitable model of AD previously we have shown that development of AD signs is accompanied by changes in expression of genes involved in neurotrophic signaling pathway. Thus in this work we investigated a link between changes in expression of neurogenesis-associated genes and development of AD-like pathology in OXYS rats.

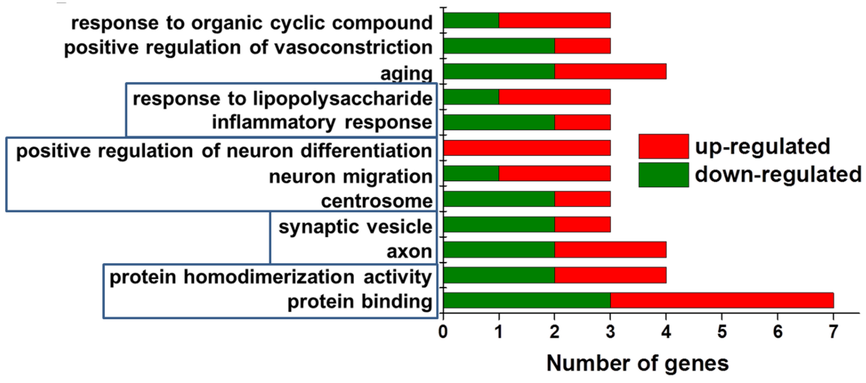
Methods and Algorithms: 20-days-, 3-5- and 18-months-old male OXYS and Wistar (control) rats were used. The RNA-seq data obtained for hippocampus were used to analyze differentially expressed genes involved in neurogenesis according to MANGO (Mammalian Adult Neurogenesis Gene Ontology) database. These genes were functionally annotated using DAVID (Database for Annotation, Visualization and Integrated Discovery). ELISA was used to quantify the levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), TrkA and p75^{NTR} receptors, western-blot analysis was used to quantify levels of TrkB and phosphorylated TrkB (phTrkB) receptors in the hippocampus.

Differentially expressed genes (DEGs) associated with neurogenesis in OXYS rats

The Venn diagram shows overlapping sets of DEGs in OXYS rats compared with Wistar rats at various ages



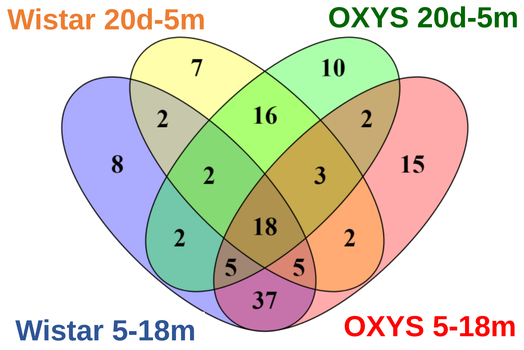
Gene Ontology terms for DEGs in OXYS rats at 18 months of age (according to DAVID)



18 months: functional annotation of DEGs in OXYS rats compared to Wistar rats (by DAVID) yields Gene Ontology terms associated with neurogenesis, synapse, protein interaction, and inflammation

Age-related changes of expression of genes related to neurogenesis in the hippocampus of OXYS and Wistar rats

The Venn diagram shows overlapping sets of DEGs in OXYS and Wistar rats at various ages

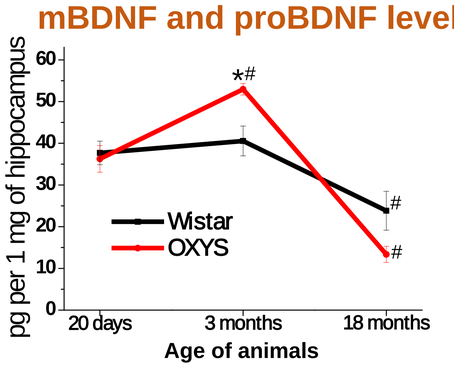


20 days – 5 months:
19 DEGs are typical only for OXYS rats
5 genes are upregulated
14 genes are downregulated
Gene Ontology terms:
positive regulation of angiogenesis
positive regulation of gene expression
response to organic substance
extracellular space

5-18 months:
22 DEGs are typical only for OXYS rats
8 genes are upregulated
14 genes are downregulated
Gene Ontology terms:
positive regulation of angiogenesis
brain development
ATP binding

Age-related changes in neurotrophic supply in the hippocampus of OXYS and Wistar rats

mBDNF and proBDNF levels



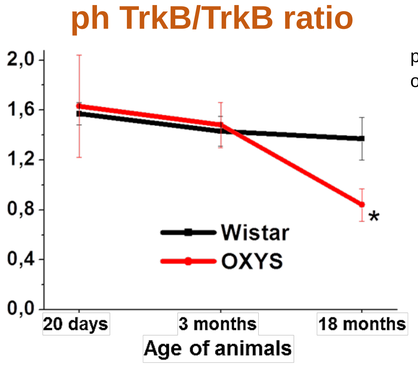
20 days: mBDNF is prevailing form of BDNF in Wistar rats and proBDNF is prevailing form in OXYS rats

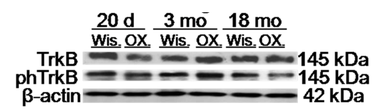
3 months: increase of the BDNF level in OXYS rats is because of increasing content of both mBDNF and proBDNF

18 months: proBDNF is prevailing form of BDNF in OXYS rats

ph TrkB/TrkB ratio

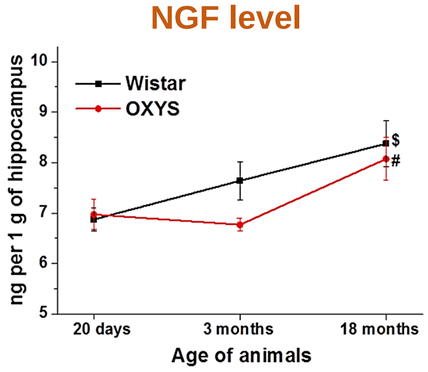
phTrkB – phosphorylated form of TrkB receptor





18 months: activation of TrkB receptor is decreased in OXYS rats

NGF level

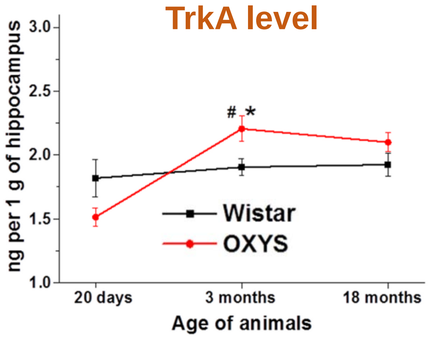


In Wistar rats, the NGF level increases from 20 days to 18 months.

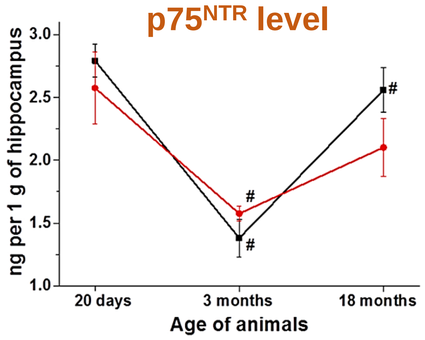
In OXYS rats, the NGF level increases only from 3 to 18 months showing a tendency to be lower at 3 months of age as compared to Wistar rats (p = 0.06).

TrkA, p75^{NTR} receptors' levels and the TrkA/p75^{NTR} ratio

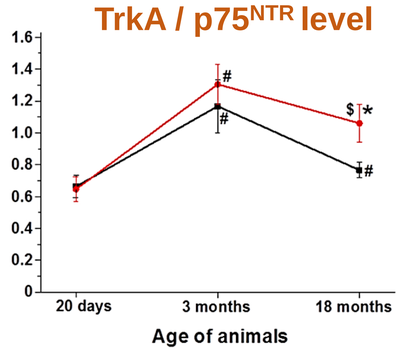
TrkA level



p75^{NTR} level



TrkA / p75^{NTR} level



* p < 0.05 for differences between strains
\# p < 0.05 for differences with previous age within a strain
$ p < 0.05 for differences with age of 20 days within a strain

20 days: peak in the level of p75^{NTR} receptor in both rat strains

3 months: the level of TrkA receptor increases in OXYS rats and becomes higher than in Wistar rats; the level of p75^{NTR} receptor significantly decreases and, as a consequence, TrkA/p75^{NTR} ratio significantly increases in both rat strains

18 months: the level of p75^{NTR} receptor and TrkA/p75^{NTR} ratio decreases in Wistar rats; the parameters in OXYS rats changes insignificantly

Conclusion: Alterations of neurotrophic supply in the hippocampus occur during development of AD-like pathology in OXYS rats and may result in disturbances of hippocampal neurogenesis

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