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The rat brain transcriptome: from infancy to aging and sporadic Alzheimer's disease-like pathology

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Motivation and Aim: It is suggested that anatomical (quantity and connectedness of neurons) and functional (capability to use alternative neural circuits) traits of adult brain – all of which are established in the early life – might impact brain susceptibility to Alzheimer's disease (AD), the most common late-life dementia. The results of our work on the senescence-accelerated OXYS rats, a unique model of sporadic AD (the most prevalent form of the disease; ~95 % of cases), have confirmed the validity of this hypothesis. We have identified the features of brain maturation in OXYS rats in the early postnatal period which can act as prerequisites for the development of initial neurodegenerative changes in the later age. It naturally follows that the events at the molecular-genetic level underlie the phenomenon of the delayed brain maturation in OXYS rats.
Methods and Algorithms: To elucidate the nature of the revealed changes in brain maturation we analyzed transcriptomes (RNA-seq data) of the prefrontal cortex (PFC) and hippocampus of OXYS and Wistar rats at the ages of P3 and P10 (P – postnatal day) – which according to our estimates is the critical period of brain maturation in OXYS rats. In addition, we performed a comparative gene expression analysis in the rat PFC and hippocampus from infancy to aging and AD-like pathology using these results and previous RNA sequencing data as comprehensive approach toward understanding the molecular genetic mechanisms for the development, aging and dementia.
Results: Analysis of transcriptomes of the hippocampus and prefrontal cortex of OXYS and Wistar rats in the early postnatal period revealed metabolic pathways and processes, changes in which contribute to the delay in brain maturation in OXYS rats. At the age of P3 and P10 in OXYS rats, the number of differentially expressed genes (DEGs) was more than 1.000 in both brain structures (Padj < 0.05); changes in the expression of more than 200 of them were unidirectional in the hippocampus and cerebral cortex at both age points. The functional annotation of the DEG indicates a reduced efficiency of the formation of neuronal contacts, insufficiency of astrocytic and microglial support, mitochondrial functions, and angiogenesis delay. Comparison of these results with the results of the transcriptomes of the hippocampus and prefrontal cortex in the period preceding the development of AD signs (age 20 days), during their manifestation (5 mo) and active progression (18 mo) made it possible to evaluate for the first time on a sporadic model forms of AD, molecular genetic prerequisites and mechanisms for the development of the disease at all its stages. Three genes Thoc3, Exosc8, and Smpd4 were identified; there expression were increased in both brain regions of OXYS rats throughout life.
Conclusion: Thus, we here demonstrated that reduced efficiency of the formation of neural networks in the brain of OXYS rats in infancy obviously contributes to the development of AD-like pathology. The reason for the delay in brain maturation may be

a decrease in the duration of gestation and reduced birth weight that were previously identified in OXYS rats. Our results raise the question that decreased duration of gestation and delayed brain development in infancy may be high risk factors for developing AD in the future.

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