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Insufficient neuronal support by glial cells as a predictor and driver of Alzheimer's disease-like pathology in OXYS rats

Stefanova N.A.[1]*, Rudnitskaya E.A.[1, 2], Burnyasheva A.O.[1], Kozlova T.A.[1], Kolosova N.G.[1]

[1] *Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

[2] *Ben-Gurion University of the Negev, Beer Sheva, Israel*

* *stefanovan@mail.ru*

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Motivation and Aim: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder and the most common cause of dementia in an aging population. Prevalence of AD dramatically increases in people aged 65 years or older. To date, there is no known medication that will stop the course of AD, which is largely due to incomplete knowledge of disease pathogenesis. Recently more attention has been given to the role of glial cells, especially microglia and astrocytes, in the process of neurodegeneration. Astrocytes are the most common type of cells in the central nervous system that perform many functions in the brain including neuronal protection and maintenance of homeostasis. Microglia are the main resident immune cells of the brain, which are involved in homeostasis and in host defense against pathogens and disorders of the central nervous system. In various pathological conditions, including AD, they go into states associated with either an increase or loss of their functions, which contributes to neuroinflammation and neurodegeneration. Currently, the influence and support of neurons by glial cells is considered as one of the possible strategies for slowing the development of the disease. Today, it is obvious that inappropriate support of neurons by glial cells plays an important role in the pathophysiology of AD. However, it is not clear whether it plays a key role in the development of the disease or is a consequence of its progression?

Methods and Algorithms: Using senescence-accelerated OXYS rats as a suitable model of AD [1] we examined the features of glial support in the hippocampus and frontal cortex during the whole life of animals: from the birth to the progressive stages of AD-like pathology. Wistar rats were used as healthy controls.

Results: We found that OXYS rats are born with lower density of astrocytes and microglial cells and higher extent of apoptosis in the hippocampus and frontal cortex compared to control Wistar rats [2]. This situation persists for all first postnatal week with the one exception at postnatal day 3: at this time point, astrocyte density in the hippocampus increased and became higher in OXYS rats than in Wistar rats, which together with significant increase of apoptosis may accompany increased neurogenesis in hippocampal dentate gyrus (DG) [2]. As for the functional state of glial cells, it was worse in OXYS rats in the first week after birth. At the second week of life the glial support normalized, and at the end of the period of brain maturation–that means, the end of the third week of life–astrocyte density became even higher in the hippocampus of OXYS rats with simultaneous increase in the apoptosis extent and intensity of neurogenesis in DG [3]. To the end of adolescence–that means, to the age of 1.5 months–astrocytic density normalized, whereas the density of microglia and, especially, its

activated fraction was higher in the hippocampus of OXYS rats compared to Wistar rats. The first signs of neurodegeneration in OXYS rats are observed at the age of 3–5 months. Interestingly, this period is not accompanied by any significant changes in glial support of the hippocampus or frontal cortex of OXYS rats. The period of amyloid-β accumulation – that means, 12 months of age – is accompanied by increased neuro- and gliogenesis in the hippocampus of OXYS rats as well as by the tendency to higher microglia density. This activation may be of compensatory nature and direct to slow down neurodegenerative processes. Activated gliogenesis at 12 months of age led to increased astrocyte density in the hippocampus at 18 months of age – at the progressive stage of AD-like pathology in OXYS rats. This increase in astrocyte density during the progression of AD signs in OXYS rats can be considered as support to the neurons and synapses against degeneration or as the sign of astrogliosis accompanying neurodegenerative changes in the hippocampus.

Different interventions can affect the course of neurodegeneration through their influence on glial support of the neurons and synapses. We examined the effectiveness of cognitive training and systemic antioxidant SkQ1 administration to normalize glial support of hippocampus of OXYS rats at the progressive stage of AD-like pathology (18 months of age). While cognitive training even increased the already higher density of astrocytes in OXYS rats, SkQ1 administration did not affect this parameter and significantly decreased the density of activated microglia cells thus exerting anti-inflammatory effect [4].

Conclusion: In general, our results indicate that the most prominent alterations in glial support of hippocampus and prefrontal cortex of OXYS rats occur in early life, at the course of brain development and maturation. These alterations contribute to neurodegenerative processes and the development of AD signs and may serve as early predictors of neurodegeneration. At the same time, altered glial support at the progressive stages of AD-like pathology in OXYS rats is more likely reactive rather than causative. Different interventions may improve glial support and as a consequence slow down neurodegeneration, however the proper time for these interventions need to be determined.

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