NMR BASED METABOLOMIC PROFILING OF BRAIN IN RAT MODEL OF ALZHEIMER'S DISEASE

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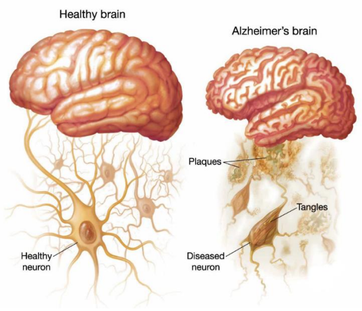
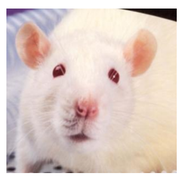
Background

The incidence of Alzheimer's disease (AD) is growing dramatically against the background of the aging of the world population. This study is aimed at the solution of an urgent scientific problem - identifying the metabolic predictors and markers for the development of the most common (~95%) sporadic form of AD. Changes in concentrations of low molecular weight metabolites reflect the disturbances in metabolic cycles during the development of Alzheimer's disease, so the identification of the most promising metabolomic biomarkers is very important from a prognostic point of view.



The study was performed with the use of the OXYS rat line, a model of early aging, one of the manifestations of which is the development of a complex of AD signs. Wistar rats of the same age were used as control. Quantitative analysis of brain metabolites of rats was carried out in the "preclinical" period preceding the development of signs of AD (at the age of 20 days), during their manifestation (3 months), and active progression (18 months).

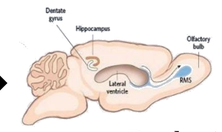
Materials and methods



OXYS
Wistar
rats

Sample preparation

Age
- 20 days
- 3 months
- 18 months



Rat brain

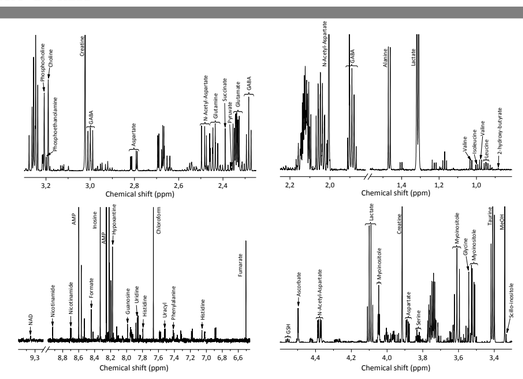
Extraction

Low molecular weight metabolites of hippocampus

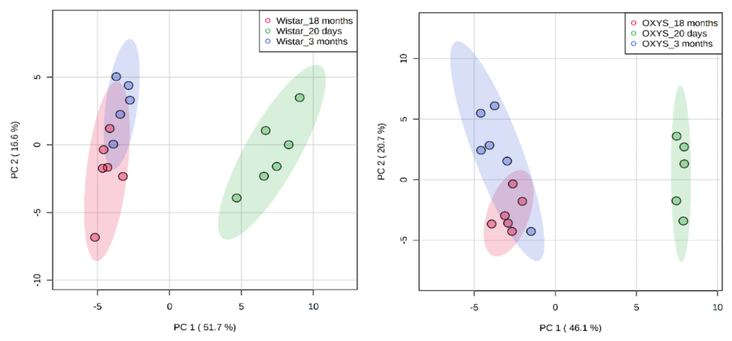
Bruker Avance III HD
700 MHz

Metabolomic profiling

Concentrations of 59 compounds in the rat hippocampus have been established, including amino acids, organic acids, antioxidants, osmolytes, glycosides, purine and pyrimidine derivatives.

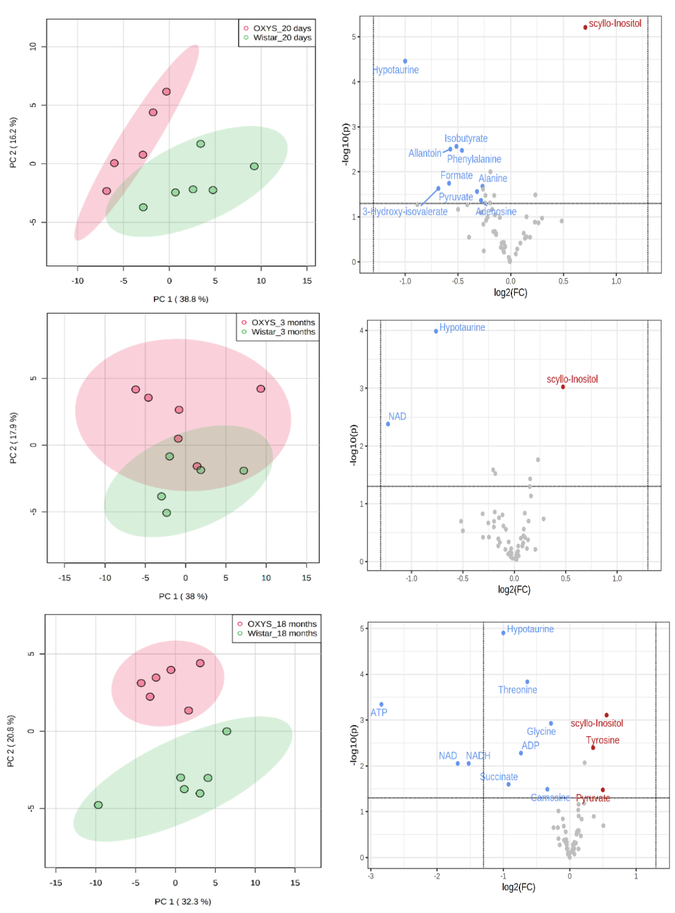


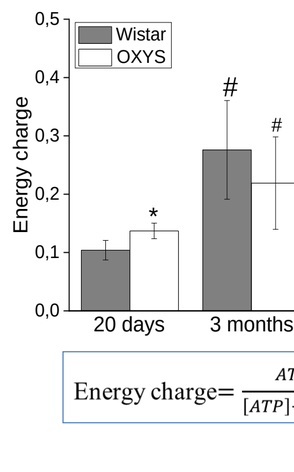
Results



Principal component analysis (PCA) of metabolomics profiles of rat brains shows sample separation. Age-related changes are explained mainly by the first component (PC1). The second component (PC2) is responsible for the difference in the samples obtained from two rats lines of the same age.

Volcano plots demonstrated that a statistically significant ($p < 0.05$, fold change > 1.2) increase was found for 1 metabolites at the initial stage of AD development (20 days, 3 months) and for 3 compounds in the active progression (18 months), while the decrease was observed for 3 (3 months) or 9 compounds (20 days and 18 months). The highest increase in concentration in all periods of AD was observed for scyllo-inositol, the decrease - for some amino acids and energy metabolites.





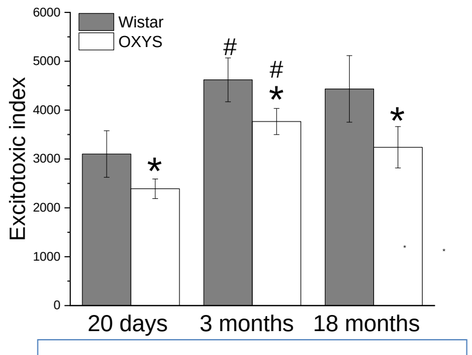
$$\text{Energy charge} = \frac{ATP + \frac{1}{2}[ADP]}{[ATP]+[ADP]+[AMP]}$$

Adenylate energy charge (AEC) of Atkinson.

The level of energy charge in rat hippocampus increases with aging. AEC was lower in OXYS rats than in Wistar rats at the age of 3 and 18 months. It was suggested that the development of AD signs in OXYS rats is accompanied by a serious deficiency in energy production in hippocampus.

The relationship between excitatory and inhibitory synaptic inputs (excitotoxic index).

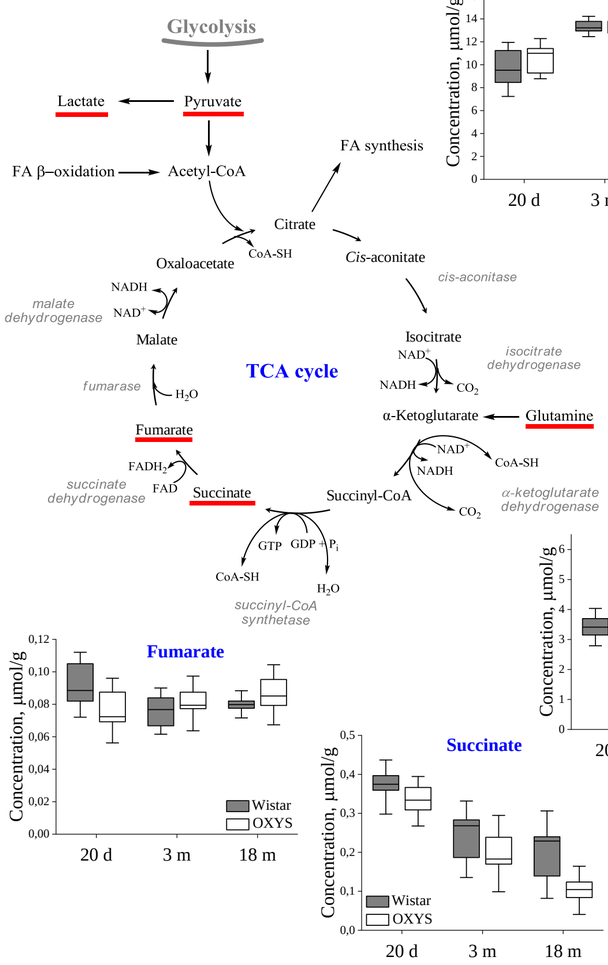
Excitotoxic index increased at the age of 3 months in both Wistar and OXYS rats, and it was lower in OXYS rats than in Wistar rats at all ages. It may indicated the prevalence of inhibitory synaptic inputs in hippocampus of OXYS rats during the development of AD signs.



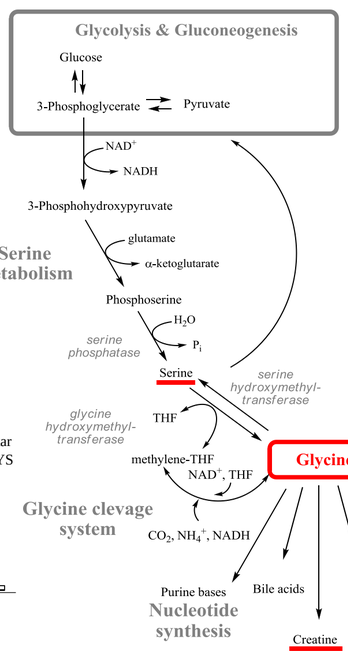
$$\text{Excitotoxic index} = \frac{[\text{Glutamate}]*[\text{Glycine}]}{[\text{GABA}]}$$

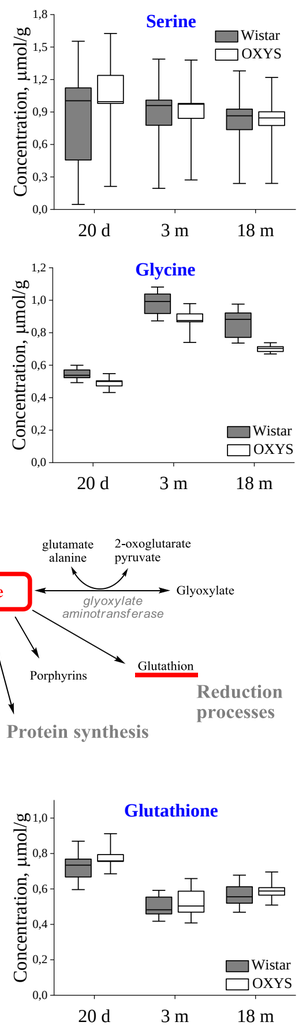
The data are presented as mean ± SEM. *p <0.05 for differences between the strains; #p < 0.05 for an effect of age.

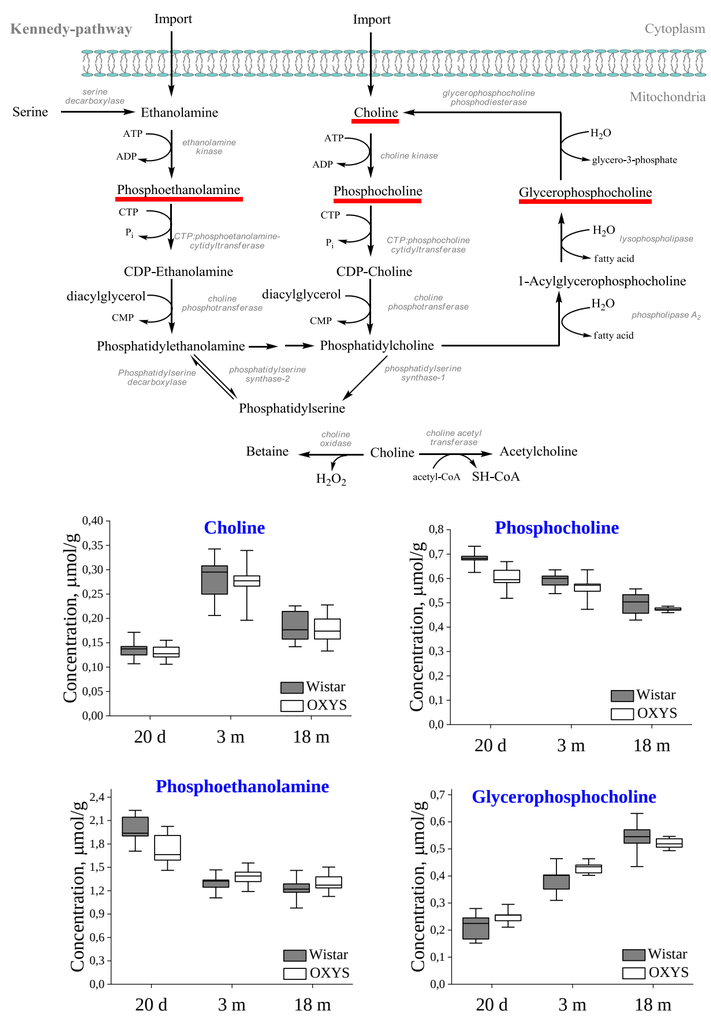
Biochemical pathways



Our results show that metabolites from the TCA cycle, glycine and choline metabolism may be potential biomarkers for the development of AD.







Conclusion

1. The general metabolic patterns of aging in the rats brain, which are involved in energy production pathways and in metabolic shifts of neurotransmitters, have been established;
2. Concentrations of inhibitory neurotransmitters (GABA-glycine) increase, while those of excitatory neurotransmitters (glutamate) decrease, especially rapidly in OXYS rats.
   Taken together, these shifts in neurotransmitter metabolism with age can impair neuronal transmission and lead to memory loss.

Future work

1. Comparative quantitative analysis of blood metabolites of rats of different age;
2. Investigation of the effect of melatonin on the relationship between the age-related features of the metabolomic profile and the development of AD signs detected in OXYS rats.

This work was supported by RSF (Project 22-24-20035)