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Alterations of glutamatergic/GABAergic systems during healthy aging and Alzheimer's disease-like pathology in rats

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Motivation and Aim: Alzheimer's disease (AD) is an incurable neurodegenerative disorder which progresses with age. Disturbance of the balance of the excitatory glutamatergic and inhibitory GABAergic systems accompanies the development of AD. However, the question of whether this dysregulation is the cause or consequence of AD development remains unanswered.
Methods and Algorithms: We used senescence-accelerated OXYS rats as a suitable AD model [1] to assess the relationship between changes in glutamatergic and GABAergic systems and the development of AD signs. Wistar rats were used as a control. The content of enzymes regulating glutamate-GABA cycle–glutaminase, glutamate decarboxylase (GAD67), glutamine synthetase (GS) and GABA-transaminase (GABA-T)–was analyzed in the hippocampus of OXYS and Wistar rats at 1.5, 4, 12, and 18 months of age by Western blot and immunohistochemistry. Additionally, the content of NMDA receptor-1 (NMDAR1), AMPA receptor-1 (AMPAR1), GABA A receptor alpha-1 (GABAAR1) and glutamate transporter-1 (GLT-1) were evaluated.
Results: We didn't observe significant age-related and interstrain changes in the levels of glutaminase and GS. Meanwhile, the level of GABA-T was lower and GAD67 was higher in OXYS rats throughout the lifespan. The level of NMDAR1 decreased with age in the hippocampus of Wistar rats; however we didn't observe this decrease in OXYS rats. Thus, NMDAR1 level was higher in OXYS rats at 18 months of age. The level of GABAR1 was higher in OXYS rats compared to Wistar rats at 3 months of age. GLT-1 level didn't change throughout the lifespan in Wistar rats, whereas in OXYS rats it increased by the age of 12 months.
Conclusion: Development of AD signs in OXYS rats occurs against background of altered balance of the glutamatergic and GABAergic systems with shift towards higher GABA levels which may contribute to the progression of neurodegeneration. Increased NMDAR1 content in OXYS rats at 18 months of age may be considered as compensation aimed to enhance glutamatergic neurotransmission at progressive stage of AD-like pathology.
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References

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