doi 10.18699/bgrs2024-13-39

Time-of-the-day–dependent alterations of glutamate/GABA system in hippocampus of rats with age and during of the Alzheimer's disease signs development

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Key words: glutamate; GABA; circadian; hippocampus; aging; Alzheimer's disease; OXYS rats

Motivation and Aim: Growing evidence suggests close correlations between Alzheimer's disease (AD) and circadian rhythm disruption. Along with cognitive impairment, circadian rhythm dysfunction is a main sing of AD. The hippocampus is a subordinate circadian oscillator. Here, more than 10 % of genes and proteins show circadian fluctuations and are associated with changes in synaptic excitability [1]. The study of circadian rhythms in the hippocampus during the development of AD is also beginning to gain momentum. Dysregulation of circadian clocks in the brain not only associated with clock genes, it may also affect neurotransmitter systems such as glutamate/GABA system. Glutamate and GABA are major excitatory and inhibitory neurotransmitters in the brain, and play a crucial role in the functioning of the hippocampus, a brain region important for learning and memory processes. But there are few studies on the diurnal variability of the glutamate/GABA system and most only analyze its variation in the suprachiasmatic nucleus [2]. There is little information on diurnal changes in the glutamatergic and GABAergic systems during hippocampus aging and even less at different stages of AD development.
In this research we analyzed the day-night variations the level of main proteins of glutamatergic and GABAergic systems in the whole hippocampus of the Wistar rats and of the senescence-accelerated OXYS rats, a model of the most common (>95 %) sporadic AD.
Methods and Algorithms: The work was carried out in the prematurely aging OXYS rats: a unique model of the sporadic form of AD. In these animals, all of the key signs of AD develop spontaneously in the absence of mutations in the *Psen1, App,* and *Psen2* genes typical of hereditary AD [3]. Animals were examined during several key periods: 20 days group corresponds to the "preclinical" period preceding the development of AD signs, during their manifestation (3 months), and active progression (18 months). Wistar rats of the same age were used as control. Animals were kept under the standard conditions of vivarium with light cycle 12-h light/12-h darkness; they received granulated feed and water *ad libitum*. Based on early data of diurnal rhythms of concentration of glutamate and GABA in rat's hippocampus, we explored two time periods – nighttime between 02.00–04.00 am and daytime between 10.00–12.00. In these time we investigeted the protein level of of glutaminase, glutaminesynthetase, GLAST, GLT1, NMDAr1, NMDA2B, GluA1, mGluR1, GAD67, GABA-T, GABAAr1, GAT1 by Western blot.
Results: Our data showed that some components of the glutamate- and GABAergic system are characterized by an increase at night and a decrease during the day in the

hippocampus of Wistar and OXYS rats at the all ages. So we detected more than 2-fold increase in subunits of NMDA receptor (subunits NR1 and NR2B; also known as GluN2B and GluN1, respectively), AMPA receptor (subunit 1 also known as GluA1) and GABA receptor (subunit alpha-1 also known as GABAAR1). Also it was observed increase at nighttime the protein level of the transporter that removes GABA (GAT1) and glutamate (GLAST and GLT1) from the synaptic cleft. While the levels of synthesis and degradation enzymes of GABA (GAD67 and GABA-T, respectively) and glutamate (glutaminase and glutamine synthetises, respectively) did not depend on the time of day in both Wistar and OXYS rats. It is important to note that protein level of NMDA and AMPA receptor subunits decreased at the nighttime in OXYS rats on the early and late stage of AD as compared Wistar rats.

Conclusion: The level of ionotropic receptor subunits and transporters of glutamate and GABA in hippocampus of Wistar and OXYS rats show variations depending on the time of day – increasing at the nigttime and decreasing at the daytime. Since these components of glutamate and GABA system are associated with synaptic plasticity, we believe that NMDA, AMPA, GABAA receptors and GABA and glutamate transporter is associated with circadian modulation of neurons and astrocytes and synaptic integration and hippocampal-dependent learning. Our data indicated that manifestation and progression of AD-like degeneration in OXYS rats accompanied by GluN2B, GluN1 and GluA1 level decreasing at the nighttime.

Funding: The study is supported by State Budget Project No. FWNR-2022-0016.

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