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Effects of amisulpride on the Tau-protein hyperphosphorilation in OXYS rats – a model of sporadic Alzheimer's disease

Naumenko V.S.*, Kondaurova E.M., Molobekova K.A., Rodnyy A.Ya.,
Stefanova N.A., Kolosova N.G.
Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia
** naumenko2002@mail.ru*

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Motivation and Aim: Alzheimer's disease (AD) is the most common cause of dementia worldwide with an increasing impact on the aging society. It is noteworthy that the percentage of people with Alzheimer's dementia increases dramatically with age: 3 % of people age 65–74, 17 % of people age 75–84 and 32 % of people age 85 or older have Alzheimer's dementia [1]. On the other hand, increasing life expectancy has been declared as one of the priorities of Russian domestic policy. Hence, development of effective therapeutic strategies against AD and AD-related disorders is among extremely topical problems of modern neuroscience and fundamental medicine.

Brain serotonin (5-HT) is a principal player in the mechanisms of brain and behavioral plasticity. Polyfunctionality of the brain 5-HT is due to a large variety of the receptors mediating 5-HT action on neurons. One of the most recently described 5-HT$_7$ receptor is involved in memory processes that require changes in synapse morphology and synaptic transmission efficiency. Stimulation of 5-HT$_7$ receptor in hippocampal neurons resulted in an increase in neurite length, dendritic projections, and synaptic density. One of the effectors responsible for this effect is CDK5. This is supported by the fact that CDK5 inhibitors blocked or reduced the density of dendritic spines, the number of which was increased upon 5-HT$_7$ receptor activation without the use of CDK5 inhibitors. It was also shown that these proteins physically interact at the plasma membrane. The fact that CDK5 plays an important role in tau hyperphosphorylation may indicate the involvement of 5-HT$_7$ receptor in tau phosphorylation status, its dissociation and further aggregation in AD. This idea was developed by the same authors who, using cellular and mouse models, showed that constitutive activation of 5-HT$_7$ receptor led, firstly, to increased CDK5 activity and, secondly, to excessive phosphorylation of the tau protein with further formation of insoluble aggregates. On the contrary, inhibition of 5-HT$_7$ receptor activity by antagonists led to the elimination of this effect [2].

To further confirm this idea, we investigated the effect of potent 5-HT$_7$ receptor antagonist on Tau-protein hyperphosphorilation and on the functional state of the brain 5-HT system in OXYS rats – a model of sporadic Alzheimer's disease – an AD form that accounts for over 95 % of cases.

Methods and Algorithms: Experiments were carried out on 1-, 3-, and 6-month old OXYS rats. Animals were treated with 5-HT$_7$ receptor agonist amisulpride (3 mg/kg, i.p.) (Solian, Sanofi-Avensis France, France) during three weeks. This drug was selected since it is already applied in clinics for psychosis treatment. After three weeks of treatment "novel object recognition" test was performed. After behavioral testing, mRNA levels were assessed using quantitative real-time RT-PCR technique. Protein

levels were estimated by Western-Blot analysis. The data were analyzed using two-way ANOVA followed by Fisher's LSD post-hoc comparison.

Results: We showed that chronic amisulpride treatment significantly affected pathological Tau-protein phosphorylation in the brain of OXYS rats. It was revealed that amisulpride administration resulted in significant reduction of the pTau/Tau ratio in the hippocampus of 3-month-old rats. Moreover, in the hippocampus of 3-month-old animals amisulpride reduced expression of CDK5 – the main kinase involved in the pathological Tau phosphorylation. Nevertheless, observed amisulpride effect on the pathological phosphorylation of the Tau-protein and CDK5 failed to affect disrupted learning behavior assessed in the "novel object recognition" test.

Additionally, we revealed anxiolytic effect of amisulpride for 3-month-old rats that is not surprising since the investigated drug is currently utilized in clinics as antipsychotic. Moreover, we showed age-dependent decrease in 5-HT_7 receptor level in the frontal cortex and hippocampus of OXYS rats. However, taking together with the published data this reduction in 5-HT_7 receptor level seems to be related to age rather than Tau-pathology. Also we found the age-related increase in Tau and pTau levels in frontal cortex and hippocampus of OXYS rats that is undoubtedly linked with Tau-pathology in investigated animals.

Conclusion: Thus, amisulpride significantly reduced pTau/Tau ratio in the hippocampus of 3-months-old OXYS rats that was accompanied by reduced expression of CDK5 – the main kinase involved in the pathological Tau phosphorylation. However, investigated drug failed to restore disrupted learning in "novel object recognition" test. Obtained results allow to conclude that 3 month is the most sensitive age for Tau-pathology treatment with 5-HT_7 receptor antagonists in OXYS rats. Additionally, we showed the age-related increase in Tau and pTau levels in frontal cortex and hippocampus of OXYS rats.

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