NMDA subunits and p62 expression in the MAM16 and neonatal MK-801 mouse models of schizophrenia

Maria Plataki [1,2], Klairi Chalkiadaki[3], Vasiliki Nikoletopoulou[2], Kyriaki Sidiropoulou [1,2]

1 Dept of Biology, University of Crete, Heraklio, Greece

2 Institute of Molecular Biology and Biotechnology-Foundation for Research and technology Hellas, Heraklio, Greece

3 Center for Discovery Brain Sciences, The University of Edinburgh, Edinburgh, UK

Plataki Maria email: maria_plataki@hotmail.com

ABSTRACT

Schizophrenia has been associated with increased oxidative stress and reduced synaptic function. Recent studies have also suggested a connection between schizophrenia and autophagy impairments. Here, we investigated the expression of NMDA receptor subunits, NR2A and NR2B, which are important for synaptic plasticity and p62, an autophagy related protein in prefrontal cortex (PFC) and hippocampus (HPC) of the MAM16, a model developed in our lab, and the neonatal MK-801 mouse models of schizophrenia.

Pregnant C57Bl/6J females received an i.p. injection of methylazoxymethanol acetate (MAM) (22mg/kg) or saline on gestation day 16. For the neonatal MK-801 model, C57Bl/6J male and female mice were injected with 0.1 mg/kg MK-801 or saline, once a day, from postnatal day(p) 11 to 15. The PFC and HPC was isolated from MAM16 and saline-treated mice at p40 and p90 and from adult (p90) neonatally MK-801-treated mice. The PFC and HPC were subjected to western blot analysis for the NR2A and NR2B subunits of the NMDA receptors and the p62 autophagy-related protein.

The NR2A and NR2B protein levels were significantly reduced in the adult HPC and PFC of both MAM16 and neonatally-MK-801, compared to their respective controls. Furthermore, reduced NR2A and NR2B levels were found in the adolescent PFC. On the other hand, p62 was significantly increased in the PFC and HPC of adult MAM-16 and neonatally-treated mice, as well as in the PFC of adolescent MAM-16 compared to controls.

Our results indicate decreased autophagy and reduced NMDA receptor expression in two different animal models of schizophrenia in adulthood. Furthermore, a similar pattern is observed in adolescent MAM-treated mice, showing that synaptic function deficits are evident before the onset of behavioral deficits.

This project is funded by the General Secretariat for Research and Technology (GSRT) and the Hellenic Foundation for Research and Innovation (HFRI)