Exposure to Enriched Environment in Adulthood Reverts Cognitive Impairment and Interneuron Deficiency Induced by Early MK801 Administration

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INTRODUCTION

One of the central questions in neuroscience is how specific populations of interneurons shift higher brain functions up to behavior. So far, we know that interneurons have a crucial role in regulating the complex interactions between principal cells, and they represent a key to the understanding of network operations. Inhibitory circuits may modify the long-term excitability of principal cells in several ways, and their synaptic plasticity can be enhanced by exposing the animals to Enriched Environment (EE).

In this study we used an animal model of schizophrenia by administering the NMDA receptor antagonist MK801. This drug induces interneuron dysfunction and cognitive impairment. We propose that a brief intervention with Enriched Environment (EE) in adulthood can be potentially beneficial to revert long-lasting learning and memory deficits, and this improvement is related to the restoration of GABAergic immunoreactivity.

MATERIAL AND METHODS

Long Evans rats were allocated in three different experimental groups. One of the groups received intraperitoneal injections of MK801 (0,5mg/kg) during P10-P20 (MK801 group), controls received the same volume of saline (VH group) and the third group received MK801 and was housed in EE from P55 until sacrifice (MK801+EE). Behavioral tasks were performed from P65 to P73. Interneurons were labeled with immunohistochemistry in hippocampus and medial prefrontal cortex, and quantified by stereological methods.

RESULTS

Decline and recovery of in cognitive abilities. EE reverts MK801 produced impairment in spatial learning and associative memory

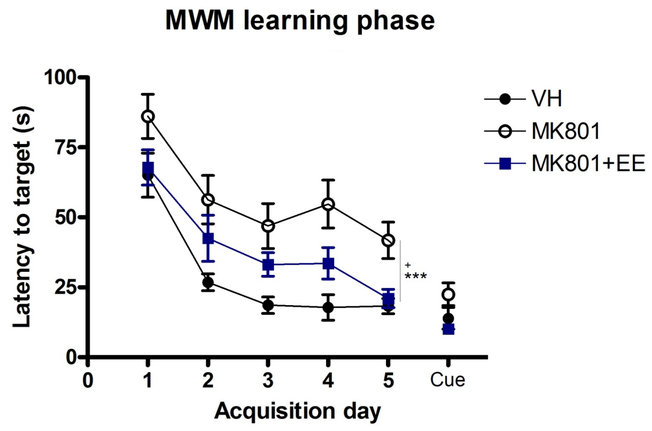


Fig. 1. Escape latencies to reach the platform during the learning process. *** p<0.001 significance VH vs. MK801. + p<0.05 significance MK801 vs. MK801+EE.

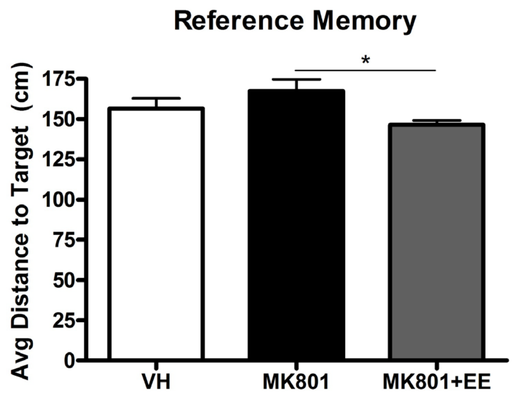


Fig. 2. Average distance to target. * p<0.05 significance MK801 vs MK801+EE.

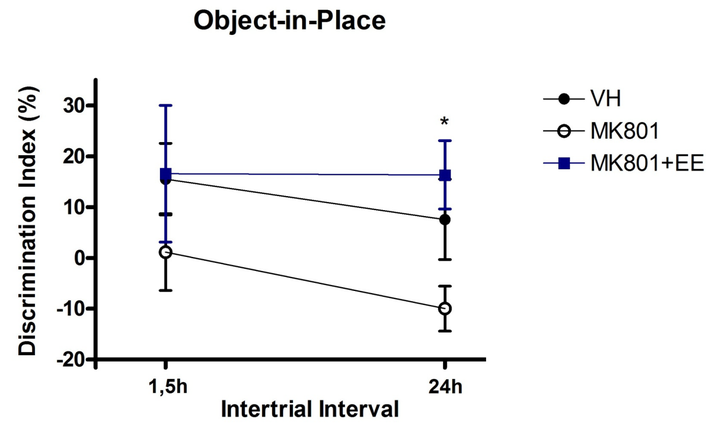
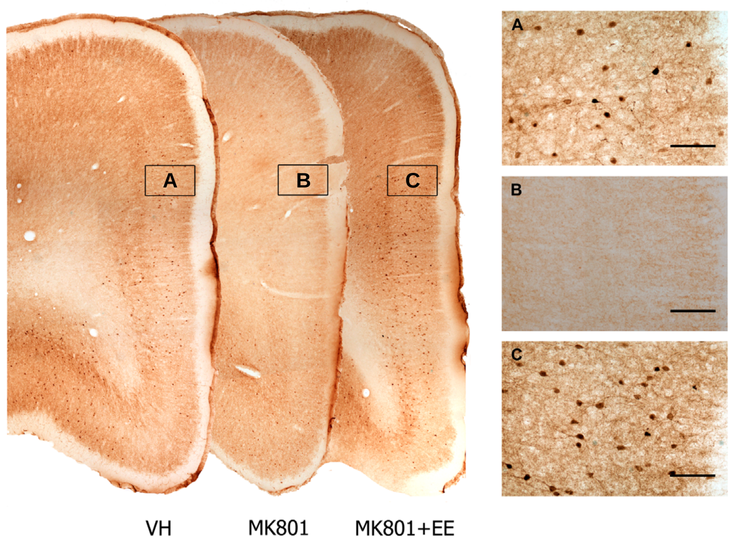


Fig. 3. Discrimination index in Object-in-Place task. * p<0.05 significance MK801 vs MK801+EE.

EE recovers PV, SST and GAD67 immunopositivity in hippocampus and medial prefrontal cortex after MK801 treatment



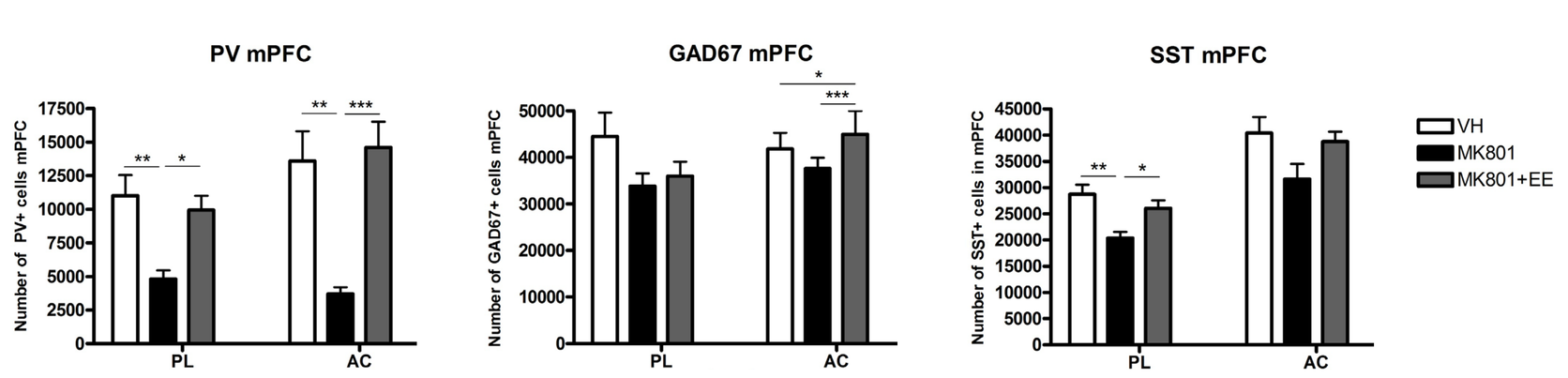
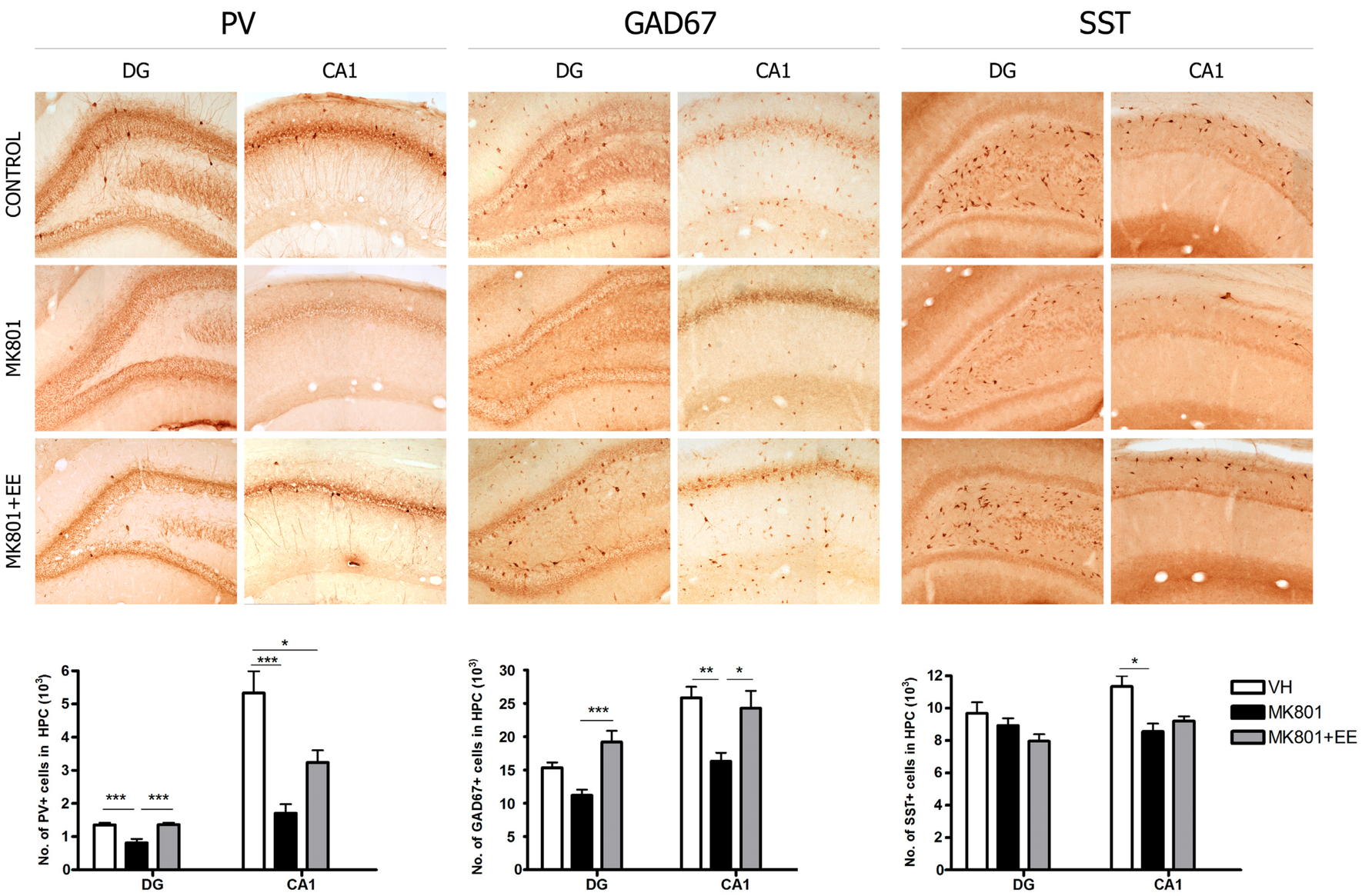


Fig. 4. Representative photographs of PV+ cells in the mPFC cortex (scale bar = 100 µm). Graphs show the number of parvalbumin (PV+), GAD67+ and somatostatin (SST+) positive cells in the medial prefrontal cortex (mPFC). Horizontal axes show different mPFC regions (PL: prelimbic; AC: anterior cingulate). Experimental groups (VH, MK801 and MK801+EE). * Significance (*p<0.05; **p<0.01; ***p<0.001).



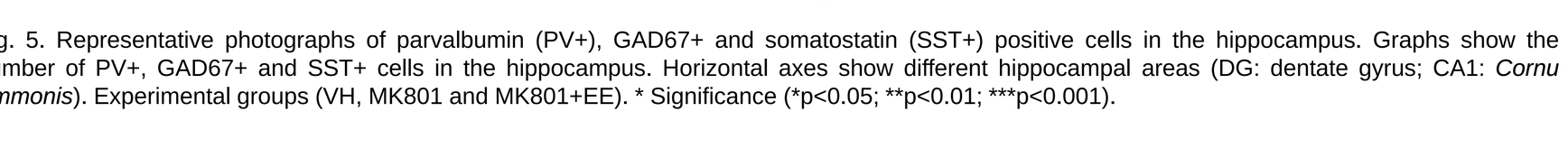


Fig. 5. Representative photographs of parvalbumin (PV+), GAD67+ and somatostatin (SST+) positive cells in the hippocampus. Graphs show the number of PV+, GAD67+ and SST+ cells in the hippocampus. Horizontal axes show different hippocampal areas (DG: dentate gyrus; CA1: *Cornu Ammonis*). Experimental groups (VH, MK801 and MK801+EE). * Significance (*p<0.05; **p<0.01; ***p<0.001).

CONCLUSIONS

- Brain circuit operations depend critically on the inhibitory tone exerted by interneurons. Interneurons temporarily organize cortical activity, and synchronization of neural activity is essential for cortical network operations and, therefore, for cognition.
- Chronic early life administration of MK801 impairs spatial learning and associative memory, as measured by Morris Water Maze and Object-in-Place task. This is accompanied by a decrease in PV immunoreactivity in HPC and in prelimibic region of mPFC of MK801-treated rats. SST expression is also significantly reduced in hippocampal CA1, and GAD67 in CA1 and Dentate Gyrus.
- Short-term (18 days) Environmental Enrichment in early adulthood is effective in reverting PV, GAD67 and SST immunoreactivity in hippocampus and mPFC, as well as the performance in behavioral tasks.

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