VALPROIC ACID TREATMENT PREVENTS THE DEVELOPMENT OF DEFICIT IN SENSORIMOTOR GATING IN ADULT PRENATALLY MAM TREATED RATS

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INTRODUCTION

Prenatal administration of methylazoxymethanol (MAM) at embryonic day 17 (E17) is considered as a neurodevelopmental model of schizophrenia [1]. Although the first symptoms of schizophrenia are seen in adults, the factors cause the risk of this disease might be present in early stage of life. The mechanism of this phenomena is still under investigation, however several data indicate that epigenetic regulation of gene expression during development might contribute to behavioral phenotypes of schizophrenia [2]. Thus, the aim of this study was to investigate whether pharmacological manipulation in epigenetic mechanisms by valproic acid (VA), an inhibitor of histone deacetylases, during pre- and post- puberty might influence the induction of schizophrenic symptoms in adults. The deficit in sensorimotor gating is a one of the psychotic symptoms and it was observed after puberty in MAM-treated animals [1]. The above disruption was chosen to determine, which period of postnatal life is critical for appearance of behavioral signs of psychosis.

METHODS

Animals and treatment

Pregnant dams (Wistar Harlan rat) were obtained from animal provider (Charles River, Germany) at embryonic day 15 (E15) and were housed individually in polycarbonate cages. They randomly assigned to the experimental groups and at E17, pregnant females were injected with 22 mg/kg/ml methylazoxymethanol acetate (MAM, Midwest Research Institute, USA) or its saline (VEH, 0.9 % NaCl, 1 ml/kg) (i.p.). The offspring were weaned 21 days after birth and only males were used in our experiments. Rats were housed by groups of five with ad libitum access to food and water with an artificial 12/12-h light/dark cycle (lights on at 7 a.m.). The different experimental groups always consisted of animals derived randomly from different litters to avoid litter effects. Experiments were conducted on rats at postnatal days 30, 45, 60, 70, 80, 90 and 120 (P30, P45, P60, P70, P80, P90 and P120, respectively). Valproic acid sodium salt (Sigma, Poland) was given at the dose 250 mg/kg, sc, twice a day, in early adolescence (23rd - 29th day), in adult before the appearance of the deficit in sensorimotor gating (63rd - 69th day) and in adult after the appearance of the deficit in sensorimotor gating (83rd - 89th day).

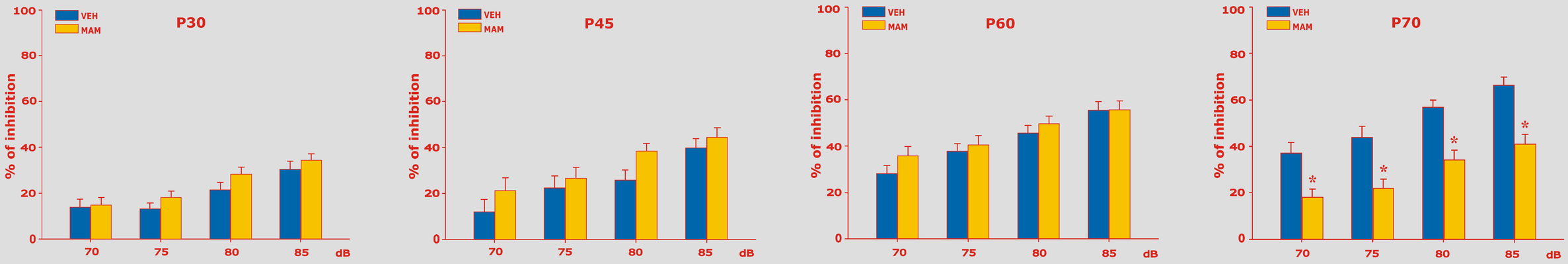
Prepulse inhibition

Efficacy of sensorimotor gating was measured by prepulse induced inhibition of acoustic startle response. Startle reactivity was measured in startle apparatus (SR-LAB, San Diego Instruments, San Diego,CA). After habituation lasting 5 min with 65 dB background white noise, two types of acoustic stimuli were used in random order: acoustic stimulus alone [(P), duration 40 ms, intensity 120 dB] or an acoustic stimulus preceded by an acoustic prepulse [(PP), duration 20 ms, intensities: 70 dB,75 dB, 80 dB or 85 dB) applied 80 ms before the stimulus (P). The degree of prepulse inhibition was shown as a percentage of inhibition (%PPI) calculated according to the following formula [(P-PP/P)]x100.

Statistics

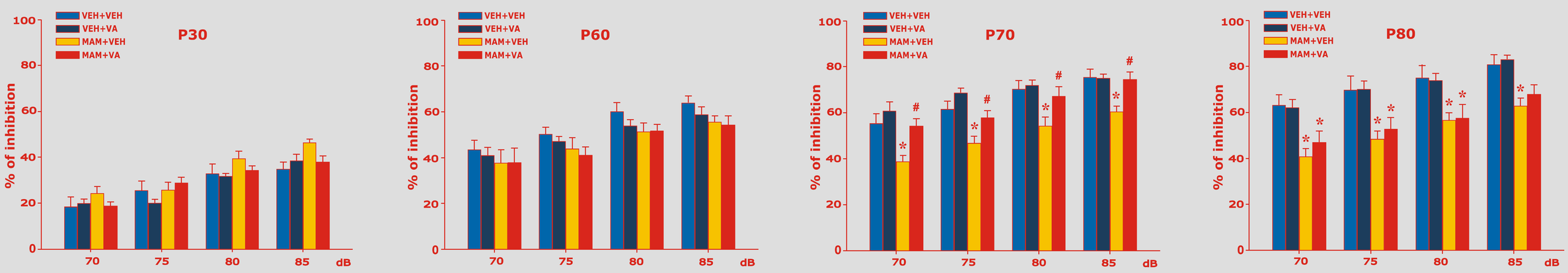
Statistical evaluation for sensorimotor gating data was performed by ANOVA for repeated measurements - type of acoustic tone as within comparison and treatmet as independent variable, followed by Newman Keuls post hoc test. All of evaluations were done in the Statistica program.

1. Sensorimotor gating in postnatal life



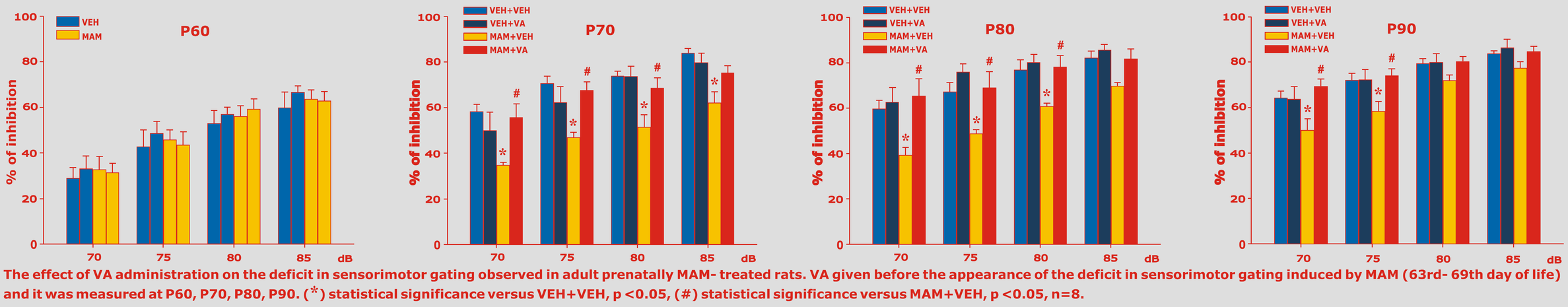
The effect of prenatal MAM administration on the sensorimotor gating in rat postnatal life measured at P30, P45, P60 and P70. (*) statistical significance versus VEH, p <0.05, n=8.

2. VA administration in early adolescence

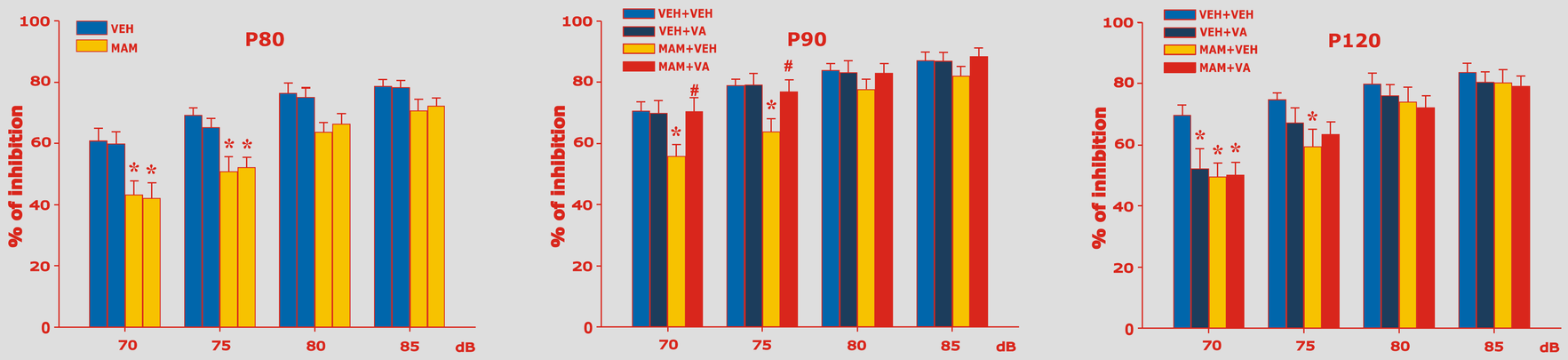


The effect of VA administration on the deficit in sensorimotor gating observed in adult prenatally MAM- treated rats. VA was given in early adolescence (23rd- 29th day of life) and sensorimotor gating was measured at P30, P60, P70, P80. (*) statistical significance versus VEH+VEH, p <0.05, (#) statistical significance versus MAM+VEH, p <0.05, n=8.

3. VA administration in adult



The effect of VA administration on the deficit in sensorimotor gating observed in adult prenatally MAM- treated rats. VA given before the appearance of the deficit in sensorimotor gating induced by MAM (63rd- 69th day of life) and it was measured at P60, P70, P80, P90. (*) statistical significance versus VEH+VEH, p <0.05, (#) statistical significance versus MAM+VEH, p <0.05, n=8.



The effect of VA administration on the deficit in sensorimotor gating observed in adult prenatally MAM- treated rats. VA was given after the appearance of the deficit in sensorimotor gating induced by MAM (83rd- 89th day of life) and it was measured at P80, P90, P120. (*) statistical significance versus VEH+VEH, p. <0.05, (#) statistical significance versus MAM+VEH, p <0.05, n=8.

REFERENCES

1. Moore, H., Jentsch, J.D., Ghajarnia, M., Geyer, M.A., Grace, A.A., 2006. A neurobehavioral systems analysis of adult rats exposed to methylazoxymethanol acetate on E17: implications for the neuropathology of schizophrenia. Biol. Psychiatry 60, 253-264.

2. Dudley, K.J., Li, X., Kobor, M.S., Kippin, T.E., Bredy, T.W., 2011. Epigenetic mechanism mediating vulnerability and resilience to psychiatric disorders. Neurosc. & Biobeh. Reviews 35, 1544-1551.

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CONCLUSIONS

The obtain data indicate that the deficit in sensorimotor gating appears only in post-puberty as it was reported by Moore et al., [1]. VA given pre-puberty only delays the appearance of deficit in sensorimotor gating in MAM-treated rats. In contrast, VA administration in post-puberty prevents the deficit evoked by MAM when was given before psychosis onset. The effect VA administration in adult after the appearance of deficit in sensorimotor gating is not sustained and disappears after 120th day of life. Thus it is conceivable that inhibition of deacetylation process in post- but not in pre-puberty might block the development of some psychotic symptoms such as impairment in sensorimotor gating.