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 causing the risk of this disease might be present in early stages of life. The mechanism of the prenatal effects of MAM is not fully understood, but experimental studies indicate that epigenetic regulation of gene expression during development might contribute to behavioral-phenotypic symptoms 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 schizophrenia symptoms in adults. The deficit in sensorimotor gating is 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 prenatal life is critical for appearance of behavioral signs of psychosis.

METHODS

Animals and treatment

Pregnant dams (Wistar-Hanen rat) were obtained from animal provider (Charissa, Rekjavik, Germany) at embryonic day 15 (E15) and were housed individually in polycarbonate cages. They were randomly assigned to the experimental groups and at E17, pregnant females were injected with 22 mg/kg i.p. methylazoxymethanol acetate (MAM, Sigma-Aldrich, St. Louis, MO, USA) or saline, 1 ml/kg (i.p.). The offspring were weaned 21 days after birth and only males were used in our experiments. Rats were housed in groups of five with ad libitum access to food and water on a 12/12-h light/day cycle (lights on at 7:00 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 20, 45, 60, 70, 80, 90 and 120 (P20, P45, P60, P70, P80, P90 and P120, respectively). (i) MAM, (ii) MAM + valproic acid (VA), (iii) saline. The effect of VA was evaluated in two periods: (a) before the appearance of the deficit in sensorimotor gating (45th - 65th day), and (b) in adult after the appearance of the deficit in sensorimotor gating (85th - 95th day).

Prepulse Inhibition

Efficiency of sensorimotor gating was measured by pre-pulse induced inhibition of acoustic startle response. Startle reactivity was measured in startle apparatus (B&L, San Diego Instruments, San Diego, CA, USA). Startle response was measured in white noise, two types of acoustic stimuli were used in random order: acoustic stimulus alone (F5), duration 40 ms, intensity 120 dB or an acoustic stimulus preceded by an acoustic pre-pulse (PP), duration 20 ms, intensity 70, 75, 80, 85, 90, 95 dB applied 80 ms before the stimulus (F5). The degree of prepulse inhibition was shown as a percentage of inhibition (%PI), calculated according to the following formula: (%PI) = 100.

Statistics

Statistical evaluation for sensorimotor gating data was performed by ANOVA for repeated measurements - type of acoustic tones as covariant treated as independent variables, followed by Newman Keuls post hoc test. All of evaluations were done in the statistics 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 VH, 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 (22nd-32nd day of life) and sensorimotor gating was measured at P30, P60, P70, P80. (*) statistical significance versus VH + 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 was given before the appearance of the deficit in sensorimotor gating induced by MAM (63rd-68th day of life) and it was measured at P60, P70, P80, P90. (*) statistical significance versus VH - VEH, p < 0.05, (**) statistical significance versus MAM + VEH, p < 0.05, n=8.

REFERENCES


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CONCLUSIONS

The obtained 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, VA treatment in post-puberty prevents the deficit evoked by MAM when it was given before psychosis onset. The effect VA administration in adult after the appearance of deficit in sensorimotor gating is not maintained and disappears after 120th day of life. Thus, it is important to determine the development of some psychotic symptoms such as impairment in sensorimotor gating.

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