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Antidepressant effects of valproic acid in an animal model of depression

Original paper

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Abstract Valproic acid, beside its anticonvulsant action, is widely used as a mood stabilizer in the therapy of bipolar disorder. The potential antidepressant action of valproic acid has not been sufficiently characterized so far. The aim of the present study was to evaluate the antidepressant effect of valproic acid in an aldosterone model of depression. Subchronic treatment with valproic acid resulted in a reduction of the time spent in immobility in the forced swim test. In conclusion, the present study provides evidence on antidepressant effects of valproic acid using a classical behavioral approach for testing the efficacy of antidepressant drug in animal models.

Keywords *sodium valproate – forced swimming test – antidepressant effect*

INTRODUCTION

Valproic acid is an antiepileptic drug used in the clinical practice for a long time. Beside its anticonvulsant action, it is widely used as a mood stabilizer in the therapy of bipolar disorder. Together with other thymoprofylactics and anticonvulsants, such as tiagabine, it also exhibits antidepressant effect (Pistovcakova et. al 2008). The exact mechanism of antidepressant action is still unknown, and therefore, it is tested in various animal models of depression (Lima et al. 2017, Qiu et. al 2015). However, the data from the literature are still insufficient to fully elucidate the potential antidepressant action of valproic acid.

The aim of the present study was to evaluate the antidepressant effect of valproic acid in an animal model of depression based on elevated circulating concentrations of aldosterone, which was shown to induce increased anxiety and depression-like behaviors (Hlavacova & Jezova, 2008; Hlavacova et al. 2012).

MATERIAL AND METHODS

Forty male adult Sprague-Dawley rats were used. Animals were housed individually in standard cages with free access to rat chow and water. All experimental procedures were approved by the Animal Health and Animal Welfare Division of the State Veterinary and Food Administration of the Slovak Republic. Animals were divided into four groups (n = 9–10 per group) based on the treatment administered. Aldosterone (d-aldosterone, Sigma, USA) or vehicle was continuously administered via subcutaneous osmotic minipumps for 14 days (Model 2002, Alzet, Alza Corp., USA). The dose of aldosterone was chosen based on our previous studies (Hlavacova & Jezova, 2008; Hlavacova et al. 2012). Simultaneously, valproic acid was administered in drinking water at a dose of 100 mg/1 kg body weight/day continuously for 14 days. Animals from placebo groups received drinking water without valproic acid.

On day 14 of the treatments, rats from each group were subjected to behavioral testing in the forced swim test to evaluate depression-like behavior. Behavioral tests were conducted during the light phase of the day, between 9.00 and 11.00 h. The rats were individually placed in a glass cylindrical tank filled with tap water (23±1°C). The testing session lasted 15 min and was videotaped by camera positioned in front of the tank. Rats behavior was scored for the last 5 min of the 15 min session (Hlavacova et al. 2012). The percentage of time which the animal spent immobile was rated as depression-like behavior (Hlavacova et al. 2018). In addition, time which animal spent struggling and swimming was also measured.

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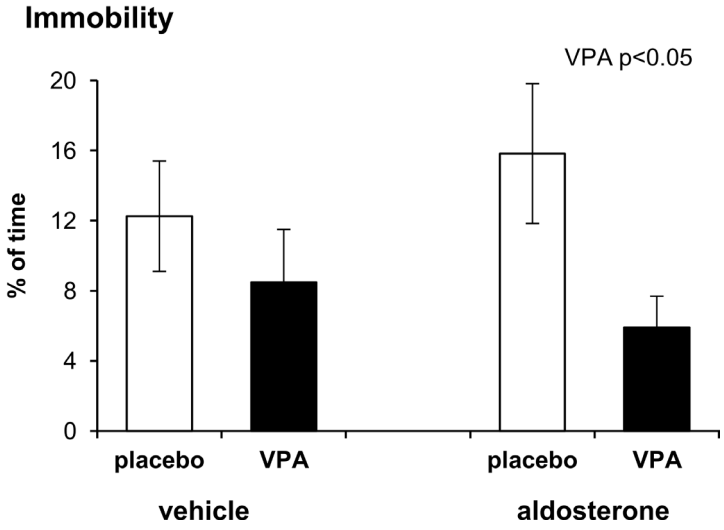

Figure 1. Time spent in immobility in forced swimming test in rats simultaneously treated with valproic acid and aldosterone. The results are expressed as means ± SEM. Overall level of significance was defined as p<0.05.

RESULTS

The data were checked for the normality of distribution using the Shapiro–Wilk test and were analyzed by two-way analysis of variance (ANOVA) for factors valproic acid (valproic acid and placebo groups) and aldosterone (aldosterone and vehicle groups).

Statistical analysis of data obtained from the forced swim test showed a significant main effect of valproic acid treatment ($F(1,34) = 5.05$, $p < 0.05$) on immobility time. Valproic-acid-treated rats spent significantly shorter time immobile compared to rats treated with placebo (Fig. 1). The animals treated with aldosterone spent longer time in immobility, but the difference did not reach significance. No significant main effects of valproic acid and aldosterone treatments or their interaction were observed in struggling and swimming behaviors (data not shown).

DISCUSSION

The present findings show antidepressant effect of sub-chronic treatment with valproic acid in aldosterone model of depression. The valproic acid is clinically used in the treatment of bipolar disorder and there are signals of its efficacy in bipolar depression (Smith et al. 2010). However, the exact experimental evidence of antidepressant effects of valproic acid is limited and contradictory.

The dose of valproic acid used in the present study was 100 mg/kg/day. The research group of Qiu and colleagues (2014; 2015) reported antidepressant-like effects of valproic acid treatment via intragastric gavage at a dose of 300 mg/kg/day in rats exposed to chronic unpredictable stress model of depression. On the other hand, the same dose of valproic acid injected intraperitoneally to mice increased the immobility in the forced swim test, indicating its depressogenic effects (Lima et al. 2017). That study revealed antidepressant effects of lower dose of valproic acid, namely, 30 and 100 mg/kg. The dose of valproic acid selected in the present study was observed to be effective in the inhibition of histone deacetylase (Bredy and Barad, 2008; Heinrichs et al. 2013) and changes in epigenetic mechanisms have been associated with the pathophysiology of depression.

Unlike our previous results (Hlavacova et al. 2012), the time spent in immobility only tended to be higher in aldosterone-treated rats. One reason for this discrepancy could be the use of Sprague-Dawley and not Wistar strain of rats in the present experiments. Another cause of the difference could be the cessation of the production of the aldosterone substance used previously by the chemical company and the need to purchase aldosterone from another company.

In conclusion, the present study provides evidence on antidepressant effects of valproic acid using a classical behavioral approach for testing the efficacy of antidepressant drug in animal models. It may be related to the epigenetic modulations induced by the same dose of valproic acid described recently (Buzgoova et al. 2019).

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