Original Contribution

EFFECTS OF RISPERIDONE ON LEARNING AND MEMORY PARAMETERS IN EXPERIMENTAL MODEL OF AUTISM

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ABSTRACT

Risperidone is the most widely used drug for treatment of irritability and aggression of children with autism. However, its effects on some cognitive parameters are not well understood.

The present study was undertaken to assess the effects of risperidone on learning and memory parameters in shuttle-box test of rats in experimental model of autism.

Our results demonstrated that administration of risperidone had beneficial effects on learning and memory of rats with experimental autism. Our data suggest the potential role of risperidone in modulating brain development, behavior and cognition in individuals with autistic features.

Key words: neurodevelopmental disorders, atypical antipsychotic, shuttle-box test, cognitive deficit

INTRODUCTION

Autism spectrum disorders (ASD) are neurodevelopmental disorders that affect about 1 in 100-150 individuals with predominant male prevalence at a boys:girls ratio of 3.5-4:1. The main features associated with autism are communication disorders, inability to establish verbal contact and stereotypical, repetitive actions and permanent disabilities in social skills. Also, most children with ASD have attention deficits, intellectual disabilities and face cognitive challenges (1, 2).

The heterogeneity of autism symptoms presents a substantial challenge to treatment. The non-pharmacological and pharmacological approaches in the therapy in ASDs aim to reduce irritability and disruptive behavior and to improve concentration, communication skills and help with educational and social development (3).

Risperidone is an atypical antipsychotic, a dopamine and serotonin receptor antagonist,

which is widely introduced in the treatment of irritability and associated symptoms in ASD patients. However the effects of risperidone on cognitive parameters are disputable (4). Aman et al, 2008 reported that risperidone did not impair cognitive-motor performance in children with autism (5). Furthermore, subsequent findings suggest beneficial effects of risperidone on efficiency of responding, activity level and behavioral tasks in children with pervasive developmental disorders (6). In addition, in another clinical study autistic children demonstrated significant deterioration in their working memory after withdrawal of chronic administration of risperidone (7).

Despite the aforementioned data are noteworthy, there are still lots of limitations in front of the clinical trials assessing the favorable effects of risperidone on cognitive parameters. The aim of the current study was to investigate the effects of risperidone on learning and memory of rats in experimental model of autism.

MATERIALS AND METHODS

Pregnant Wistar rats were maintained under standard laboratory conditions (12 h light-dark cycle, temperature 20±0,5°C, humidity 65±1%). On gestational day 12.5 the rats were intraperitoneally treated with physiological

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solution or valproic acid (VPA) (600 mg/kg) to develop the experimental model of autism. The male offspring rats were separated from the mothers on the 23rd postnatal day and divided into 4 groups, each of them consisted of 6 animals: 1. Control “C” (physiological solution, p.o.); 2. Control+risperidone “C+Risp” (1 mg/kg, p.o.); 3. Autistic “A” (physiological solution, p.o.); 4. Autistic+risperidone “A+Risp” (1 mg/kg, p.o.). The valproic acid and risperidone were of finest grade and were ordered from Sigma[®] company. The substances were administered to the animals for 21 days and shuttle box active avoidance test was performed in 5 consecutive days at the end of the period. An automatic reflex conditioner for active avoidance “shuttle box” (Ugo Basile) was used. The apparatus consisted of a standard rectangular shuttle-box with Plexiglas walls, the floor of which was a stainless-steel grid floor. The box was divided into two compartments with a plate. There was a hole in the bottom of the plate through which rats could shuttle freely. The automatically counted parameter were latency time (accumulated time before the rat crossing in the other compartment while the stimuli are on) and number of errors (no crossing in the other compartment as a response to both unconditioned and conditioned stimuli). The test parameters were automatically

registered. The results were presented as $AVG \pm SEM$, ANOVA test was used for statistical evaluation of relative changes. $P < 0,05$ was considered statistically significant. The experiments were carried out in accordance with the Bulgarian regulations on animal welfare and in conformance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). BAFS license №154/11.11.2016

RESULTS

On the first day of the learning sessions we have established prolonged latency time in the groups of rats with experimental autism (A) 205.08 ± 2.3 sec and rats with experimental autism and application of risperidone (A+Risp) 233.1 ± 2.3 sec in comparison to the control rats (C) 195.5 ± 2.2 sec ($p < 0.01$). On the fifth day rats with experimental autism (group A and group A+Risp), still showed longer latency time compared to the control groups: 173.3 ± 3.3 and 176.0 ± 6.4 sec v.s. 163.0 ± 5.6 sec, $p < 0.05$, (**Figure 2**) but it was shorter than that on the first day (**Figures 1, 2**). The most significant shortening of the latency time in the period between the first and the fifth day of the learning session is demonstrated by the “autistic” rats treated with risperidone (A+Risp) where latency time was decreased by $75.2 \pm 2.7\%$, $p < 0.01$ in comparison to group A.

Figure 1. Latency time in shuttle-box test on the first day of the learning sessions.

** $P < 0,001$ vs control group

On the first day of the learning sessions the number of errors was significantly less in rats treated with risperidone (**Figure 3**). In control group C and C+Risp group the number of errors was: 19.0 ± 0.41 and 12.5 ± 1.63 , $p < 0.01$.

There were no considerable differences in the number of errors on the fifth day between control rats and rats with experimental autism (**Figure 4**).

Figure 2. Latency time in shuttle-box test on the fifth day of the learning sessions.
* $P < 0,01$ vs control group

Figure 3. Number of errors in the shuttle-box test on the first day of the learning sessions.
* $P < 0,02$ v.s. control group

Figure 4. Number of errors in the shuttle-box test on the fifth day of the learning sessions.

DISCUSSION

The results of the present study demonstrated that the experimental rats in this model of autistic disorder had considerably disrupted learning and memory parameters, evaluated in the shuttle-box test. Administration of risperidone improved the cognitive deficit registered in the experimental animals. During the learning sessions the “autistic” group treated with risperidone demonstrated the most significant shortening of the latency time in the shuttle-box. Moreover, the number of errors done by the control rats treated with risperidone was statistically decreased. Our data suggest that chronic treatment with risperidone has beneficial effects on parameters of learning and memory of rats in experimental model of ASD.

These findings are in agreement with other reports which show modulation of neuronal development and improvement of cognitive parameters after administration of atypical antipsychotics (8, 9).

Despite thousands of studies on ASD and apart from the common belief that it develops from an interaction between genetic and environmental factors, the etiopathogenesis of autism still remains uncertain. Given the increasing prevalence of autistic symptoms, effective preventive and treatment measures should be taken. Although there still remain significant barriers to development of experimental models of ASD, the animal models are very essential for discovering of etiopathogenic mechanisms and successful treatments for symptoms of neuropsychiatric diseases. In the VPA model, the VPA administration during the fetal development disrupts the physiological neurodevelopmental process and leads to aberrant neuroplasticity which is associated with behavioral and cognitive abnormalities similar to autistic symptoms (10).

Alterations in neurotrophic factors, dysregulation of immune and metabolic brain functions and presence of neuroinflammatory changes have been associated with environmental insults in prenatal life of patients with ASD (11). Interestingly, in the last decade research studies have focused on the significant disruption of the typical synaptic maturation and plasticity in autism. Recent reports suggest that dysfunctional neuroplasticity contributes to the pathophysiology and features of ASD (12, 13). Furthermore, experimental data demonstrate

that antipsychotic treatment may have beneficial effects by improving neurogenesis and synaptic neurotransmission in particular brain regions (14, 15). In addition, it has been shown that risperidone might be effective in treating cognitive dysfunctions associated with schizophrenia (9).

Our results demonstrated that administration of risperidone improved parameters of learning and memory of rats with experimental autism and support the abovementioned data.

Risperidone is routinely used for treatment of tantrums, irritability and aggressive behavior of autistic patients. However, its effects on cognitive abilities are not well understood. The results presented here, indicate that risperidone might be useful for improving learning and memory impairment in ASD. Taken together, our data imply new perspectives in the therapy of autistic symptoms.

CONCLUSION

Treatment with risperidone had beneficial effects on learning and memory measures of rats with experimental autism. Our data suggest the potential role of risperidone in modulating brain development, behavior and cognition. A further understanding of the mechanisms of action of the atypical antipsychotic agent in autistic disorder might be suggested for developing of new therapeutic approaches for neurodevelopmental disorders.

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