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Research article

Lithium and valproate prevent methylphenidate-induced mania-like behaviors in the hole board test

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HIGHLIGHTS

- Lithium and valproate prevented the methylphenidate-induced hyperlocomotion in mice.
- Methylphenidate-treated mice mimic cardinal symptoms of mania in the hole board.
- Lithium prevented risk-taking and goal-directed behaviors induced by methylphenidate.

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ABSTRACT

Manic bipolar is diagnosed by psychomotor agitation, increased goal-directed activity, insomnia, grandiosity, excessive speech, and risky behavior. Animal studies aimed to modeling mania are commonly based in psychostimulants-induced hyperlocomotion. The exploration of other behaviors related with mania is mandatory to investigate this phase of bipolar disorder in animals. In this study, the hole board apparatus was suggested for evaluating mania-like behaviors induced by the psychostimulant methylphenidate. The treatment with methylphenidate (10 mg/kg, ip) increased locomotion in the open field test. The pretreatment with lithium (50 mg/kg, ip) and valproate (400 mg/kg, ip) significantly prevented the hyperlocomotion. In the hole-board test, methylphenidate increased interactions with the central and peripheral holes and the exploration of central areas. Lithium was more effective than valproate in preventing all the behavioral manifestations induced by the psychostimulant. These findings were discussed based on the ability of methylphenidate-treated mice mimicking two symptoms of mania in the hole board test: goal-directed action and risk-taking behavior. In conclusion, the results point to a new approach to study mania through the hole board apparatus. The hole board test appears to be a sensitive assay to detect the efficacy of antimanic drugs.

1. Introduction

Bipolar disorder is a chronic mental illness defined by the alternation of manic and depressive periods with euthymic or normal mood states between episodes [1]. The estimated lifetime prevalence of bipolar disorder in general population is around 4% [2]. The onset of first manic or depressive episode in young adulthood frequently occurs above the 25 years old [2]. It is still unknown the etiology of bipolar disorder, but probably genetic and environmental factors are involved [3,4].

Modeling bipolar disorder in animals is extremely challenging given the difficulty to infer mood states that mimics the clinical symptoms and cognitive deficits of human illness [5,6]. On top of the difficulties to modeling bipolar disorder in animals is the oscillating nature of the disease [7], in which patients alternate between episodes of depression and mania/hipomania [1]. While depressive symptoms include anhedonia, lack of motivation, loss of appetite, insomnia, motor retardation or agitation, fatigue, cognitive impairment, and suicidal thoughts, a manic episode is characterized by expansive or irritable mood, increased goal-directed activity, psychomotor agitation, excessive speech, grandiosity, insomnia, distractibility, involvement with risky activities and flight of ideas [1]. In this way, animal models for the entire scope of bipolar disorder are in fact non-existent and the common practice is to use distinct tests for depressive- and mania-like behaviors [5,6].

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Pharmacological treatment for bipolar disorder has two main scopes: episodes' treatment or maintenance. During depressive or manic episodes, the treatment aims to resolve an episode that is ongoing [8]. In this case, for acute mania, the pharmacological options of treatment include lithium or valproate plus an antipsychotic, while for acute bipolar depression, therapeutic options more frequently used are atypical antipsychotics [9]. In maintenance treatment, the focus is to delay the occurrence of future episodes, and minimize the severity of episodes that do occur [8]. Lithium and valproate are the most efficient monotherapies for the long-term treatment of bipolar disorder [9]. Thus, considering animal models of bipolar disorder, it is expected that these drugs can prevent and/or normalize the behavioral parameters which are mimicking a human bipolar episode [6,10].

Different experimental approaches including animal models that singly evaluate each phase of bipolar disorder, *i.e.*, depression and mania, have been used. Modeling depression is similar to what happen in the context of experimental major depression, in which behavioral despair tests, such as forced swimming test and tail suspension, can be used [11]. Differently, modeling mania may be more challenging since many symptoms are exclusively observed in human beings, which limit the approach [12,13]. The induction of hyperactivity in response to drugs that modulate dopaminergic activity is the most common [14]. The psychostimulant methylphenidate has been reported as a pharmacological tool to induce hyperactivity related to a manic-like state in mice [15–18]. However, psychostimulants-induced hyperlocomotion cannot be directly addressed to mania, once this manifestation can be observed in animal models of other psychiatric disorders, *i.e.* schizophrenia [19].

Mimicking one or more of mania symptoms in rodents rather than hyperactivity would be mandatory to refine the investigation of the biological basis and the treatment targets of this psychiatric disorder. In this context, the present study aimed to propose the hole board test as a novel tool to study mania-like behaviors in mice. The first-line mood stabilizers lithium and valproate were used to pharmacologically validate the methylphenidate-induced behaviors in the open-field and hole board tests.

2. Material and methods

2.1. Animals

Experiments were conducted using male Swiss mice breaded at the Federal University of Rio Grande do Norte (Natal, Brazil) (12–16 weeks old, 28–35 g). Mice were housed in plastic cages (41 × 34 × 16 cm) in groups of maximum 13 per cage under standard conditions (22 °C;12-h light:12-h dark cycle, lights on at 6:00 am) with food and water *ad libitum*. A total number of 160 mice were used to develop this study. All experiments were conducted in accordance with Brazilian Law No. 11.714/2008 for care and use of experimental animals. The protocol was approved by Ethic Committee for Animal Use of Federal University of Rio Grande do Norte (Licenses No. 040/2012; 041/2014). This study is reported following the ARRIVE guidelines [20].

2.2. Drugs and treatments

Methylphenidate (Novartis Biociências S.A., São Paulo, Brazil), sodium valproate (Sanofi S.A., São Paulo, Brazil) and lithium (Sigma-Aldrich Corporation, St. Louis, MO, EUA) were used. All the drugs were dissolved in saline solution. Methylphenidate (10 mg/kg) was administrated 15 min prior to the tests, while sodium valproate (400 mg/kg) and lithium (50 mg/kg) were injected 30 min before methylphenidate injection. All the drugs were intraperitoneally (ip) administrated in a volume of 10 ml/kg and were freshly prepared before experiments. Control groups were treated with saline solution following the same schedule described to treatment groups. The drugs employed in this study have been previously reported in the literature, either to induce mania-like behavior (methylphenidate) or to prevent it in rodents (sodium valproate and lithium) [16–18].

2.3. Methylphenidate-induced hyperlocomotion in the open-field test

Hyperlocomotion induced by methylphenidate was measured in the open-field apparatus, which consisted of a wooden box covered with black impermeable formica (40 × 40 × 40 cm). The test room had a controlled illumination (dimly-light condition; approx. 50 lx at the center of the apparatus). Each mouse was placed in the center of the apparatus and the distance travelled (in meters) were measured by a video camera connected to an automated activity monitoring system (AnyMaze, Stoelting Co., Wood Dale, IL, USA) for a period of 30 min. After the behavioral evaluation of each mouse, the arena was wiped with water-alcohol (5%) solution.

2.4. Hole board test

Measures of hole board parameters were performed in a wooden box (40 × 40 × 35 cm) with 16 holes (3 cm of diameter) on the ground: 4 in the center and 12 in the periphery of the board. The board was suspended 5 cm to the floor. Detailed description of the hole board apparatus is illustrated in Fig. S1. Each animal was evaluated for a period of 10 min. During this time, the frequency of interactions with the central and peripheral holes, the time spent in (in s) and the distance moved (in meters) in the central area was measured. Behaviors like sniffing or poking the hole for at least 1 s were recorded as interactions with the holes. The distance moved and the time spent in the central area was recorded by a video camera connected to an automated activity monitoring system (AnyMaze, Stoelting Co., Wood Dale, IL, USA). The interactions with the holes were manually recorded by an experienced observer who was blind with respect to the treatment conditions.

2.5. Statistical analysis

Data were analyzed using Student *t*-test or one-way ANOVA followed by Duncan's test, as specified in the legends, and were presented as mean ± SEM of n animals. Differences were considered significant when $p < 0.05$. All statistical analyses were performed using the softwares Prism version 5.0 (Graphpad Software Inc, San Diego, USA) and Statistica version 7.0 (Statsoft Inc, Tulsa, USA).

3. Results

3.1. Effect of methylphenidate on the mouse exploratory behavior in the open field and hole board tests

As shown in the Table 1, the behavioral pattern of mice treated with methylphenidate was significantly different from the exhibited by controls in the open field and hole board tests. Treatment with the psychostimulant drug significantly increased the cumulative distance travelled in the open field test ($t = 5.32$, $df = 15$, $p < 0.05$). Concerning the hole board assay, methylphenidate induced a significant increase in the central and peripheral holes interaction (central interactions: $t = 2.59$, $df = 28$, $p < 0.05$; peripheral interactions: $t = 2.27$, $df = 28$, $p < 0.05$). In addition, methylphenidate-treated mice explored more the central areas of the hole board compared to saline group (central distance