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Effect of repeated sodium valproate and topiramate administration on mania-like behaviors induced by methylphenidate in mice

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Novel and effective treatments for mania are needed, and well-validated animal models are important to reach this goal. The psychostimulant-induced hyperactivity is the most frequently animal model of mania used. Although this model is validated pharmacologically using mood stabilizers, data about its predictive validity with negative controls (i.e., drugs that are clinically ineffective in treating mania) are lacking. The present study evaluated the effects of the repeated administration of a clinically effective drug (sodium valproate) and clinically ineffective drug (topiramate) on methylphenidate (MPH)-induced manic-like behaviors in Swiss mice in the behavioral pattern monitor (BPM). Methylphenidate increased locomotor activity and center activity in the BPM. Valproate attenuated the effect of MPH on locomotor and general activity, with no effect on center activity. Topiramate did not affect any MPH-induced manic-like behaviors. Methylphenidate did not change exploratory activity (rearing or nose poking). These results support the predictive validity of MPH-induced hyperactivity for screening antimanic-like drugs.

Key words: animal model, anticonvulsant, mania, mice, psychostimulant, validity

INTRODUCTION

Bipolar disorder (BD) is a chronic, debilitating, and severe mental illness that typically consists of both manic and depressive episodes that are usually separated by periods of euthymia (Goodwin and Jamison, 2007; American Psychiatric Association 2013). BD affects approximately 45 million people worldwide (World Health Organization 2018), with annual direct healthcare costs in the United States of nearly $30 billion and indirect costs of above $120 billion (Disalver, 2011). Approximately one-third of BD patients attempt suicide, which has been associated with a high mortality rate (Novick et al., 2010).

Carbamazepine, valproate, lithium, and antipsychotics have been the main treatments for acute mania (Cipriani et al., 2011). Although sodium valproate/valproic acid/divalproex and carbamazepine effectively treat mania, topiramate and lamotrigine did not show a better response than placebo as a monotherapy (Cipriani et al., 2011; Yildiz et al., 2015).

Animal models are useful tools for screening putative new drugs for psychiatric disorders. Psychostimulant-induced hyperactivity is the most frequently animal model used to study mania (Young et al., 2011). Hyperactivity is observed in 90% of patients during manic episodes and it is frequently used as a primary outcome to assess the validity of animal models of mania (Einat,

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2006; Goodwin and Jamison, 2007; Young et al., 2011; Sharma et al., 2016; de Miranda et al., 2017). In this line, methylphenidate (MPH)-induced hyperactivity has been used as an animal model of mania in mice (Barbosa et al., 2011; Pereira et al., 2011; Shanthakumar et al., 2013; Tonelli et al., 2013; Souza et al., 2016; Kanazawa et al., 2017; Asth et al., 2020). Its primary pharmacological actions involve DAT and norepinephrine transporter (NET) inhibition (Heal et al., 2013). In healthy volunteers (without psychiatric disorders), MPH induced manic-like mood changes (Smith and Davis, 1977). Moreover, MPH triggered mania in bipolar patients without the concomitant use of mood stabilizers, although it did not affect patients who used mood stabilizers (Viktorin et al., 2017). This clinical data indicated that MPH is an interesting drug for a translational model of mania. Acute MPH-induced hyperlocomotion model of mania has been validated with clinically effective drugs (lithium, sodium valproate, carbamazepine, tamoxifen, and antipsychotics), supporting its positive predictive validity, i.e., ability to detect potential effective drugs (Barbosa et al., 2011; Pereira et al., 2011; Tonelli et al., 2013; Souza et al., 2016; Nogoceke et al., 2016; Kanazawa et al., 2017; Asth et al., 2020). However, the negative predictive validity (ability to detect ineffective drugs) is also an important property of animal models to avoid/reduce false-positive results. In this line, only one study evaluated the effect of diazepam in MPH-induced hyperactivity (Kanazawa et al., 2017).

Although hyperactivity is the main readout of manic-like behavior, the inclusion of other mania-like features could refine these models. Thus, exploratory activity, risk-taking behavior, movement patterns, aggressive behavior, distractibility, increase sexual drive, and ultrasonic vocalizations have been proposed to improve animal models of mania (Einat 2006; 2007; Young et al., 2011; Wendler et al., 2016; Wöhr, 2021). The behavioral pattern monitor (BPM) for mice has been used to expand the profile of manic-like behaviors, evaluating simultaneously locomotor and exploratory behaviors in the same subject (Young et al., 2011). BPM was used to evaluate the effects of GBR12909, a dopamine transporter (DAT) inhibitor, and amphetamine administration to C57BL/6 mice and the manic-like behavior of DAT knockdown mice (van Enkhuizen et al., 2013; 2014; Milienne-Petiot et al., 2017; Kwiatkowski et al., 2019; Cope et al., 2021). However, no study evaluated the effect of MPH on the behavior of Swiss mice evaluated in BPM.

The objective of the present study was to evaluate the predictive validity of MPH-induced manic-like behaviors using clinically effective (sodium valproate; positive control) and ineffective (topiramate; negative control) drugs for mania. In addition, it was also studied the behavioral pattern in BPM of Swiss mice treated with MPH. It was expected that MPH induced manic-like behaviors on BPM and that repeated valproate administration (but not topiramate) blocked the effects of MPH.

METHODS

Animals and environment

Eighty-four male Swiss mice (90-105 days old), weighing 35-50 g, were used in this study. The mice were housed in groups of five in polycarbonate cages (29 cm × 9 cm × 12 cm) on a 12 h/12 h light/dark cycle (lights on at 7:00 AM) with controlled room temperature (21°C ± 1°C). Food and water were provided *ad libitum*. Animals were allowed to acclimate to these conditions for at least 7 days before the study. All of the experimental procedures were performed according to current Brazilian Law for Animal Experimental Ethics and Care (11.794/8, October 2008) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The institutional Ethical Board approved the experimental protocol (CEUA-UFPR, protocol no. 1241). All efforts were made to reduce the number of mice used and their suffering.

Drugs

Sodium valproate (Depakene®, Abbott, Rio de Janeiro, Brazil) and MPH (Ritalina®, Novartis, São Paulo, Brazil) were prepared in 0.9% saline. Topiramate (Sigma, MO, USA) was dissolved in Tween-80 and reverse osmosis water and vortexed for 30 s. Sodium valproate (100 and 200 mg/kg) and topiramate (16 and 30 mg/kg) and their respective vehicles were administered intraperitoneally (i.p.) once daily for 21 days. Methylphenidate (10 mg/kg) was administered 20 min before the mice were placed in the BPM. All drugs were administered in a volume of 0.1 ml/10 g body weight.

The sodium valproate doses were based on previous studies (Flaisher-Grinberg and Einat, 2010; Barbosa et al., 2011), which did not cause any locomotor changes in an open field in a pilot study (data not shown). The topiramate doses were based on a previous study that reported a decrease in immobility time in mice in the forced swim test (Bourin, 2009). The MPH dose was based on a pilot study in our laboratory that observed a significant increase in locomotor activity in the BPM (data not shown).

Experimental design

The mice were randomly distributed into experimental groups using Calculator Soup online calcu-

lator (https://www.calculatorsoup.com/index.php). The home cage was not considered for this randomization. Different groups of mice were treated with sodium valproate (100 or 200 mg/kg), topiramate (16 or 30 mg/kg), or their respective vehicles. On the day of the experiment, each group was randomly subdivided into two groups: half received MPH 20 min before the experiment, and the other half received vehicle.

Each test drug had six experimental groups (n=7-10 mice/group): valproate experiment: (I) vehicle+vehicle, (II) vehicle+MPH, (III) 100 mg/kg sodium valproate+vehicle, (IV) 100 mg/kg sodium valproate+MPH, (V) 200 mg/kg sodium valproate+vehicle, and (VI) 200 mg/kg sodium valproate+MPH; topiramate experiment: (I) vehicle+vehicle, (II) vehicle+MPH, (III) 16 mg/kg topiramate+vehicle, (IV) 16 mg/kg topiramate+MPH, (V) 30 mg/kg topiramate+vehicle, and (VI) 30 mg/kg topiramate+MPH.

All the mice were naive to the BPM, and they were used only once. The experiments were performed during the light phase of the light/dark cycle.

Behavioral tests

Locomotor activity, exploratory behavior, and risk-taking behavior were examined in the BPM (Systel Information Technology, Curitiba, PR, Brazil), adapted for mice as described by Young and collaborators (2007; Perry et al., 2009). The device consisted of a light- and sound-attenuating wooden outer box with openings in the cover for allow internal ventilation. This box was painted black inside, with an internal white light (300 lux in the center, 90 lux in the four box corners). The internal box was a Plexiglas arena (30.5 cm × 61 cm × 38 cm) with eight holes in the walls (three in each long wall and one in each short wall; 1.25 cm diameter, 1.9 cm above the floor) and three-floor holes with the same size. Each hole contained an infrared beam to detect hole poking. Two sets of photo beams were used to detect activity every 0.1 s. One set of sensors was located 1 cm above the floor (2.5 cm apart) and used to record transitions. The other set of the 16 sensors (2.0 cm apart) was located 10 cm above the floor and used to record rearings. The position of the mouse was defined across nine unequal regions (four corners, four walls, and center; Fig. 1). The session began by placing the mouse in the bottom left corner of the arena. Each session lasted 60 min. All the sessions were recorded by a GoPro7white camera (Wetech Industrial Corp., Ltd., Shenzhen, Guangdong China).

The four BPM readout assessments were (1) number of transitions (locomotor activity), (2) number of rearings, which included both on- and off-wall rearings (exploratory behavior), (3) number of holepokes (exploratory behavior), and (4) center entries (number of entries) in the center square of the arena (risk-taking behavior). A new variable was recently introduced, a composite index of general activity, which sums the number of photobeam interruptions of any kind that are registered during the session (Kwiatkowski et al., 2021). Moreover, in the present study, we also computed the exploratory index, which is the sum of the number of rearings and the number of holepokes.

Statistical analysis

First, it was evaluated the effect of MPH on BPM behaviors by comparing the vehicle+vehicle group with the vehicle+MPH group in valproate experiment and topiramate experiment independently using Student's t-test. Next, the data of each experiment were analyzed using a one-way analysis of variance (ANOVA) followed by a planned contrast test. Pairwise comparisons of interest were planned *a priori* between the vehicle+vehicle group and the sodium valproate or topiramate+vehicle and vehicle+MPH groups and between the vehicle+MPH group and sodium valproate or topiramate+MPH group. All the statistical analyses were performed using Statistica 7.0 software (StatSoft, Tulsa, USA). Values of $p<0.05$ were considered statistically significant. The data are expressed as mean + SD.

Effect size is used as a measure of the biological, behavioral, and clinical significance of experimental results (Cohen, 1992; Lakens, 2013). Thus, the effect size of valproate and topiramate administration on locomotor activity was calculated using an online calculator for Hedges *g* (https://www.socscistatistics.com/).

RESULTS

Effect of acute methylphenidate on behavioral pattern monitor behaviors

Methylphenidate led to the expected enhancement of transitions compared with vehicle in valproate experiment (t_{13}=-5.936, $p<0.001$; Fig. 2A) and topiramate experiment (t_{12}=-4.512, $p<0.001$; Fig. 2B). Methylphenidate induced more center entries compared with vehicle in valproate experiment (t_{13}=-4.700, $p<0.001$; Fig. 2C) but not in topiramate experiment (t_{12}=-1.727, $p>0.05$; Fig. 2D). Methylphenidate increased the general activity index in valproate experiment (t_{13}=-3.570, $p<0.01$;

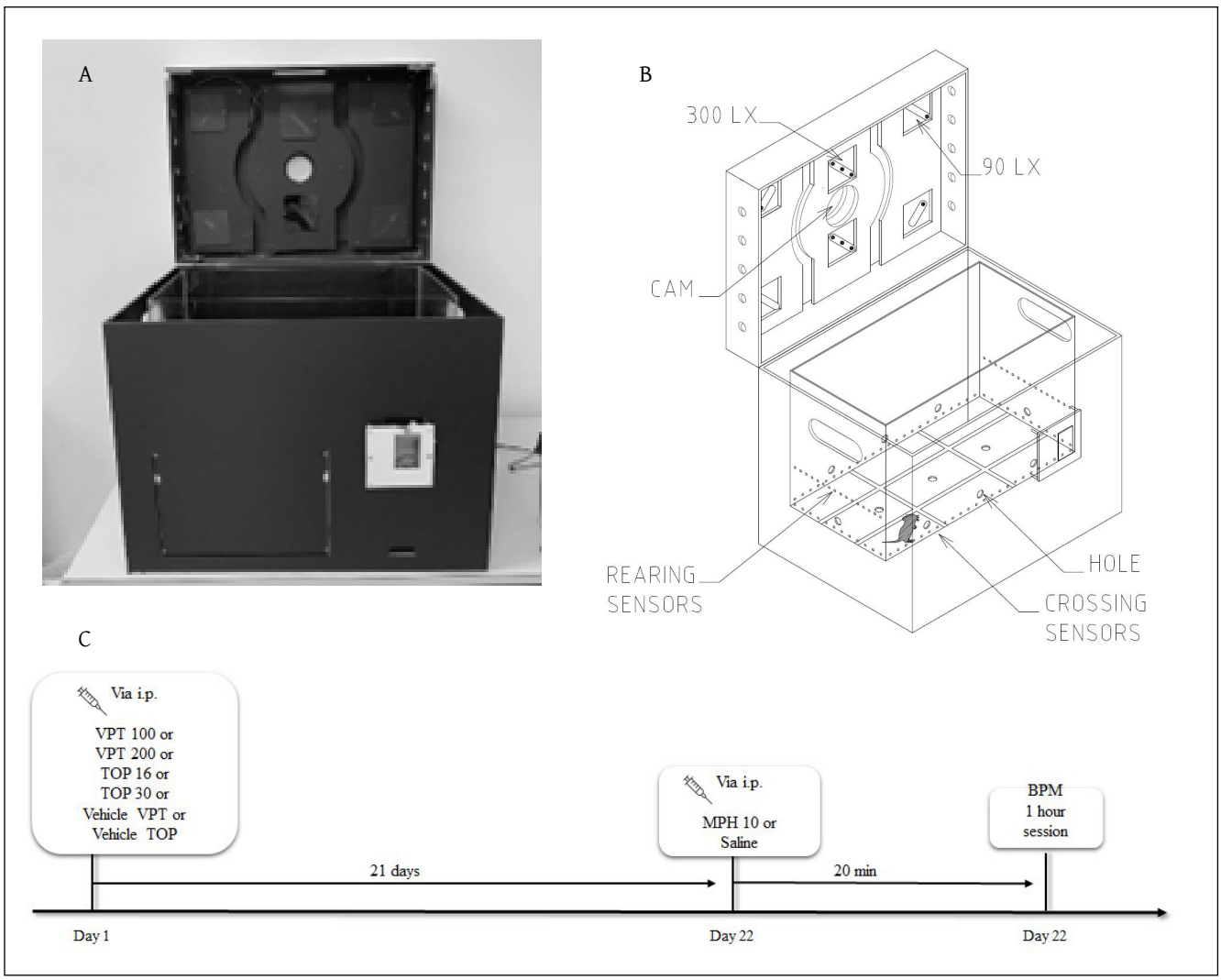

Fig. 1. (A) and (B) Behavioral pattern monitor for mice – BPM (Systel Information Technology, Curitiba, PR, Brazil); (C) Experimental Design. VPT 100 = Valproate (100 mg/kg), VPT 200 = Valproate (200 mg/kg), TOP 16 = Topiramate (16 mg/kg), TOP 30 = Topiramate (30 mg/kg), MPH 10 = Methylphenidate (10 mg/kg), BPM = behavioral pattern monitor.

Fig. 2E) and topiramate experiment (t_{12}=-4.796, p<0.001; Fig. 2F). Methylphenidate did not significantly alter the number of holepokes, number of rearings, or exploratory index compared vehicle in either experiment (all t between 0.300 and -1.432, p>0.05; Fig. 3).

Effect of 21-day treatment with sodium valproate or topiramate on acute effects of methylphenidate on behavioral pattern monitor behaviors

The ANOVA revealed a significant difference among groups of sodium valproate treatment ($F_{5,37}$=7.377, p<0.001; Fig. 2A) and topiramate treatment ($F_{5,42}$=6.772, p<0.001; Fig. 2B) on the number of transitions. In mice treated with MPH, pretreatment with 200 mg/kg sodium valproate decreased transitions compared with vehicle (p<0.05), whereas pretreatment with 100 mg/kg sodium valproate did not attenuate the effect of MPH on transitions (p>0.05 compared with the MPH+vehicle group). Topiramate (16 and 30 mg/kg) did not prevent MPH-induced alterations of transitions compared with the vehicle+MPH group.

The ANOVA revealed a significant difference among groups of sodium valproate treatment ($F_{5,37}$=3.441, p<0.05; Fig. 2C). Mice that were treated with 200 mg/kg sodium valproate alone exhibited an increase in center entries compared with the vehicle+vehicle group (p<0.05). Sodium valproate (100 and 200 mg/kg) did not reverse MPH-induced changes in center entries com-

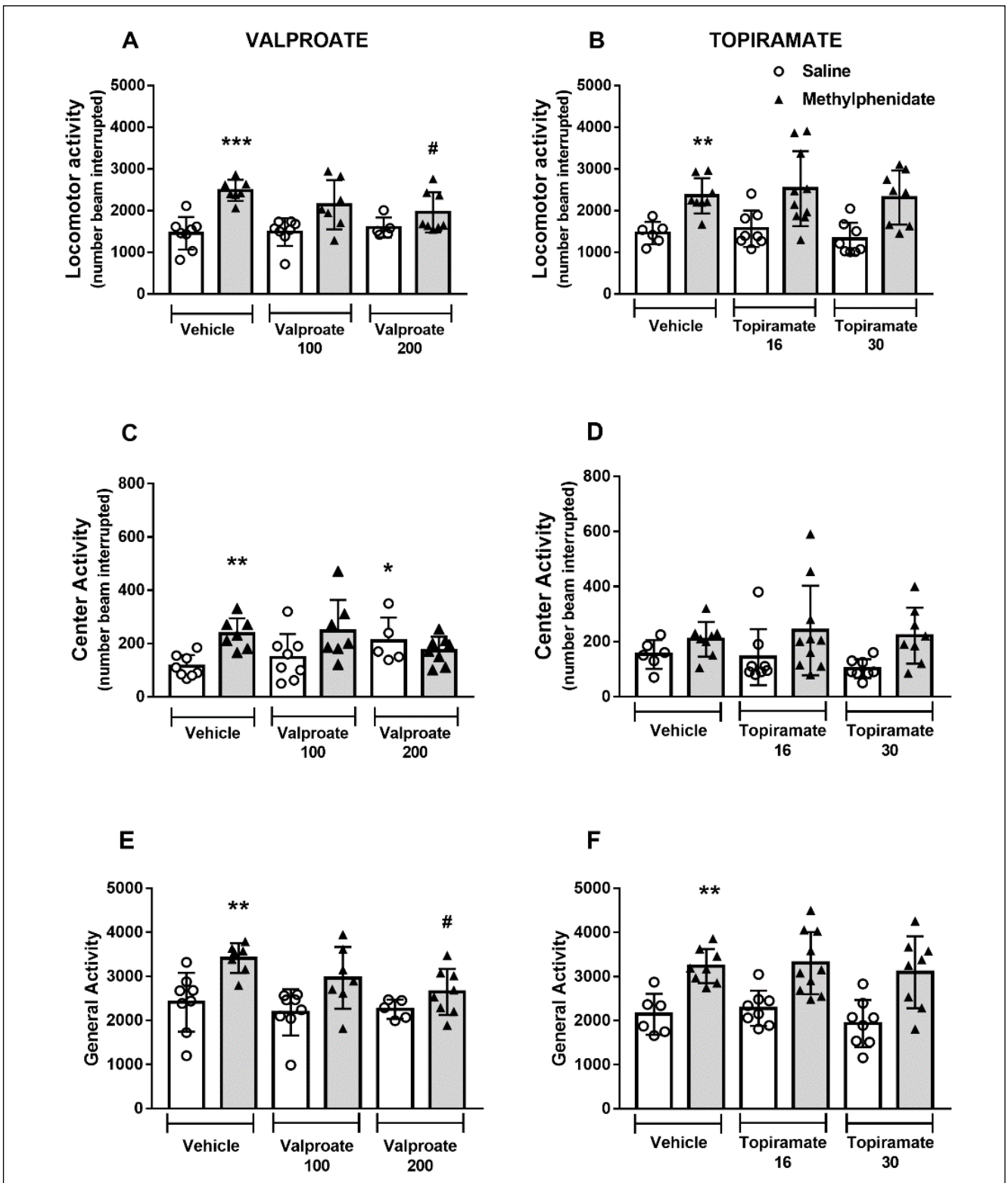

Fig. 2. Effects of repeated sodium valproate (100 and 200 mg/kg) and topiramate (16 and 30 mg/kg) treatment for 21 days on methylphenidate – MPH (10 mg/kg)-induced mania-like behaviors in mice in the behavioral pattern monitor in a 60-min session. (A) Total number of transitions for valproate treatment. (B) Total number of transitions for topiramate treatment. (C) Total number of center entries for valproate treatment. (D) Total number of center entries for topiramate treatment. (E) General activity for valproate treatment. (F) General activity for topiramate treatment. The data are expressed as mean + SD. *n* = 7-10 mice/group. **p*<0.05, ***p*<0.01, ****p*<0.001, *vs*. vehicle+vehicle; #*p*<0.05, *vs*. vehicle+MPH.

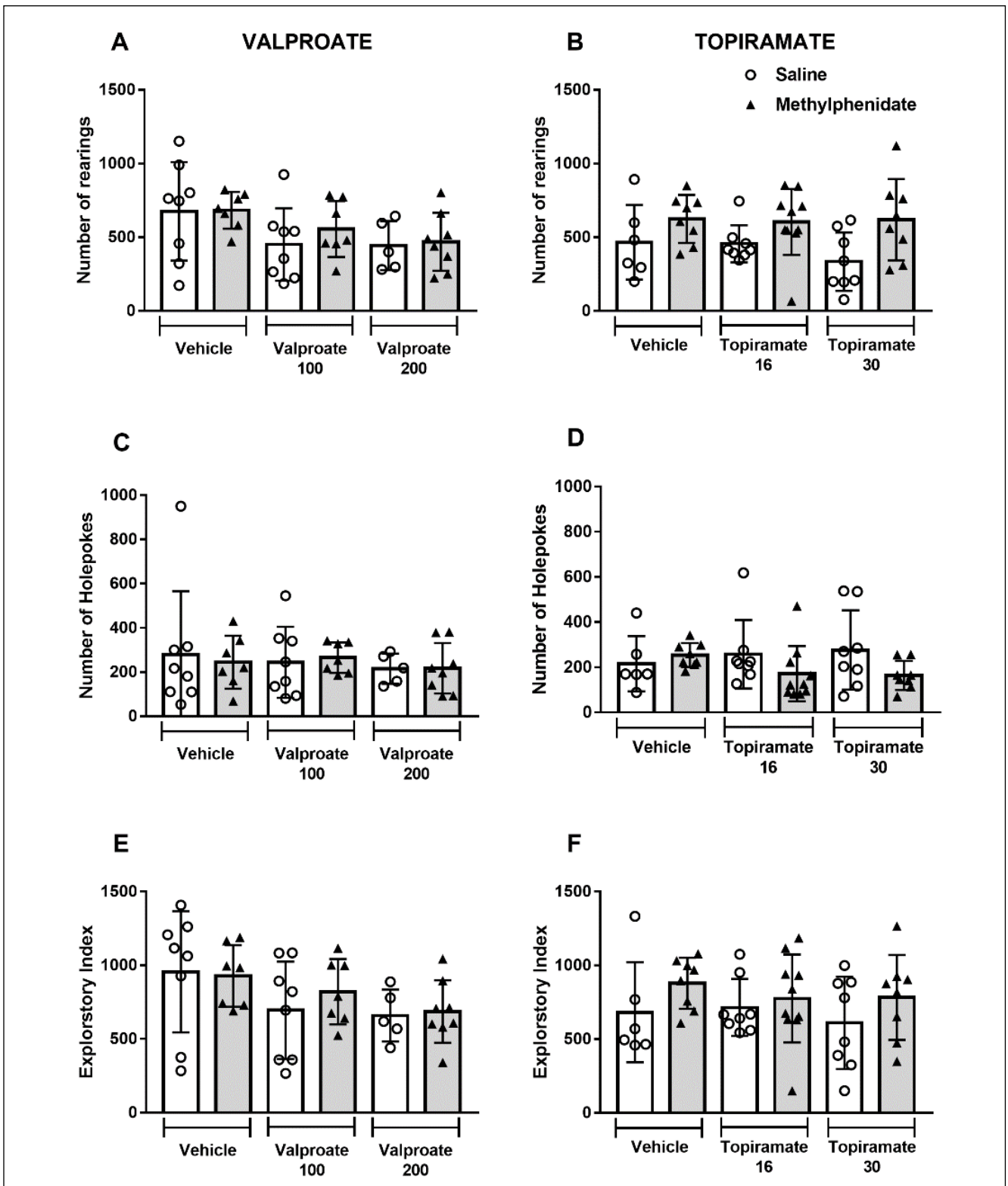

Fig. 3. Effects of repeated sodium valproate (100 and 200 mg/kg) and topiramate (16 and 30 mg/kg) treatment for 21 days on methylphenidate – MPH (10 mg/kg)-induced mania-like behaviors in mice in the behavioral pattern monitor in a 60-min session. (A) Total number of holepokes for valproate treatment. (B) Total number of holepokes for topiramate treatment. (C) Total number of rearings for valproate treatment. (D) Total number of rearings for topiramate treatment. (E) Exploratory Index (holepokes + rearings) for valproate treatment. (F) Exploratory Index (holepokes + rearings) for topiramate treatment. The data are expressed as mean + SD. n = 7-10 mice/group.

pared with the vehicle+MPH group. No significant effect among groups on topiramate treatment was found ($F_{5,42}$=2.334, p>0.05; Fig. 2D).

The ANOVA revealed a significant difference among groups of sodium valproate treatment ($F_{5,37}$=5.324, p<0.001; Fig. 2E) and topiramate treatment ($F_{5,42}$=8.873, p<0.001; Fig. 2F). In mice treated with MPH, pretreatment with 200 mg/kg sodium valproate decreased general activity compared with vehicle (p<0.001), whereas pretreatment with 100 mg/kg sodium valproate did not attenuate the effect of MPH on general activity compared with the MPH+vehicle group. Topiramate (16 and 30 mg/kg) did not prevent MPH-induced alterations of general activity compared with the vehicle+MPH group.

The ANOVA revealed a significant difference among groups of topiramate treatment on rearings ($F_{5,42}$=2.513, p<0.05; Fig. 3D). The planned contrast test did not show significant differences in the number of rearings between groups for either treatment in the *a priori* planned comparisons. The ANOVA revealed no significant difference among groups of sodium valproate treatment ($F_{5,37}$=1.713, p>0.05; Fig. 3C).

The ANOVA revealed no significant difference among groups of sodium valproate treatment ($F_{5,37}$=0.173, p>0.05; Fig. 3A) or topiramate treatment ($F_{5,42}$=1.259, p>0.05; Fig. 3B) on holepokes.

The ANOVA revealed no significant differences among groups of sodium valproate treatment ($F_{5,37}$=1.506, p>0.05; Fig. 3E) or topiramate treatment ($F_{5,42}$=0.913, p>0.05; Fig. 3F) on exploratory activity.

The effect of valproate on MPH-induced hyperactivity had a Hedges' g of 1.27, whereas topiramate had a Hedges' g of 0.07.

DISCUSSION

The present study evaluated the predictive validity of MPH-induced manic-like behaviors using clinically effective (sodium valproate) and ineffective (topiramate) drugs for mania. Sodium valproate prevented the MPH-induced increase in transitions and general activity, without affecting center entries. Topiramate did not impact the effects of MPH on transitions or general activity. Regarding MPH effects on BPM, although it increased transitions and center entries (measures of hyperactivity and risk behavior), rearings or holepokes (measures of exploratory behavior) were not affected.

Previous meta-analyses showed that valproate effectively treats mania (Cipriani et al., 2011; Yildiz et al., 2015). Nearly all studies that evaluated antimanic-like effects or validated different animal models of mania used sodium valproate and lithium as positive controls (Shanthakumar et al., 2013; van Enkhuizen et al., 2013; 2015; Arunagiri et al., 2014; Souza et al., 2016; Asth et al., 2020). In the present study, pretreatment with sodium valproate prevented the MPH-induced increase in transitions, without affecting the increase in center entries. This effect was seen at a dose that did not impair spontaneous locomotor activity, as expected for an antimanic drug (Young et al., 2011). Van Enkhuizen et al. (2013) reported that chronic valproate treatment reduced hyperactivity but did not affect specific behaviors or behavioral organization in BPM. In an automatic activity chamber, repeated sodium valproate administration blocked MPH-induced hyperlocomotion in Swiss albino mice (Barbosa et al., 2011). Interestingly, in the present study, sodium valproate treatment did not prevent the MPH-induced increase in risk-taking behavior, which is consistent with a previous preclinical study (Souza et al., 2016). Valproate was also ineffective to reduced center entries of DAT knockdown mice in BPM (van Enkhuizen et al., 2013). On the other hand, valproate was effective in reduced center entries in C57BL/6 mice treated with GBR or submitted to sleep deprivation (van Enkhuizen et al., 2013, Dal-Pont et al., 2019, Varela et al., 2021). However, an increase in center activity has been related to risk-taking behavior (Barbosa et al., 2011; van Enkhuizen et al., 2013; Souza et al., 2016; Varela et al., 2021), but it is also associated with a decrease in anxiety (Prutt and Belzung, 2003; Bach, 2022). Valproate alone increased center activity in the BPM, which may be associated with its anxiolytic-like effect (Dalvi and Rodgers, 2001; Dombrowski et al., 2006). In the present study, this anxiolytic-like effect of valproate may counteract the antimanic-like effect of valproate on the reduction of center activity. Further studies are needed to clarify this issue. On the whole, these results indicated the positive validity of the model.

Regarding topiramate, previous meta-analyses showed that it was not clinically effective for the treatment of acute mania in bipolar patients (Cipriani et al., 2011; Yildiz et al., 2015). As expected, in the present study, topiramate did not exert an antimanic-like effect in the MPH model. In this line, topiramate also failed to attenuate methamphetamine-induced stereotypy (Tatsuta et al., 2007). Since topiramate decreased immobility time in mice in the forced swim test at the same dose that was used in the present study (Bourin et al., 2009), it could be suggested that the doses used here are pharmacologically active. Thus, the topiramate results indicate that MPH-induced manic-like behaviors in the BPM can discriminate between anticonvulsants that are effective (valproate) and ineffective (topira-

mate) for the treatment mania, indicating its good predictive validity.

Effect-size comparisons also reinforce this conclusion. The effect of valproate on locomotor activity showed a large effect size, whereas topiramate's effect exhibited a very small effect size (Cohen, 1992; Lakens, 2013). The absence of a statistically significant effect of topiramate in topiramate experiment could be attributable to the relatively low statistical power of the experiment. However, the statistical power for locomotor activity in both experiments (valproate and topiramate) was greater than 0.90 (G*Power 3.1.9.6 software; Faul et al., 2007). These data support the conclusion of the absence of an antimanic-like effect of topiramate in the present study.

MPH increased locomotor activity and risk-taking behavior, which is consistent with previous studies showing a reduction of DAT activity in mice evoked mania-like behaviors (Perry et al., 2009; Young et al., 2007; van Enkhuizen et al., 2013; Kwiatkowski et al., 2019; 2021; Cope et al., 2021). However, MPH did not alter exploratory behavior in the BPM, which contrasts with observation in the holeboard apparatus (Souza et al., 2016). This discrepancy could be attributable to differences in the apparatus (hole diameter) protocol (repeated handling for drug administration), different apparatus, apparatus luminosity, and differences in holepoke definitions).

Reductions of dopamine transporter (DAT) function in mice by genetic knockdown (DAT knockdown mice) or pharmacological manipulations (GBR12909 administration) produced behavioral patterns in mice in the BPM that mimicked to manic patients. Both mice with DAT inhibition and manic patients exhibit an increase in activity and exploration, and a decrease of spatial *d* in the BPM (Young et al., 2007; Perry et al., 2009; Minassian et al., 2011). Some of these effects on BPM apparatus could be attenuated or reversed by clinically effective antimanic drugs, such as valproate, lithium, and antipsychotics, thus conferring positive predictive validity to the model (van Enkhuizen et al., 2013; 2014; Milienne-Petiot et al., 2017; Cope et al., 2021). However, most BPM studies did not evaluate negative controls (clinically ineffective drugs for mania) in their predictive validation protocols. Moreover, these inductions models have some practical and theoretical limitations. For example, genetically modified animals are expensive to create and not widely available, and the absence or reduction of specific protein function may lead to neuroadaptations that add confounding factors to interpretations of the results (Lin, 2008). Furthermore, the different genetic backgrounds that are used to generate DAT knockdown mice can influence behavior in the BPM (Kwiatkowski et al., 2019). Regarding the GBR12909, its ability to induce manic-like features in humans has not yet been evaluated, which complicates the translation of GBR12909 effects to bipolar patients.

The primary pharmacological actions of MPH involve DAT and NET blockade, which increases dopamine and norepinephrine levels in the synaptic cleft. The affinity of MPH for the DAT is nearly 10-fold higher than for the NET (Wenthur, 2016). However, in the frontal cortex, where DAT density is low, NET is important to DA uptake (Moron et al., 2002). Dopaminergic neurotransmission on frontal cortex has a significant role in mania pathophysiology (Ashok et al., 2017). Thus, MPH is an interesting tool to study DA mediation of manic-like behaviors in animal models. In humans, MPH triggers manic episodes in bipolar patients and induces manic-like features in normal volunteers (Smith and Davis, 1977; Viktorin et al., 2017). These effects in bipolar patients can be prevented or attenuated by mood stabilizers (Viktorin et al., 2017). Acute methylphenidate induces hyperactivity and other mania-like behaviors in mice, and these effects are sensitive to lithium, valproate, carbamazepine, and tamoxifen, which are clinically effective antimanic drugs (Barbosa et al., 2011; Cipriani et al., 2011; Pereira et al., 2011; Tonelli et al., 2013; Yildiz et al., 2015; Nogoceke et al., 2016; Souza et al., 2016; Kanazawa et al., 2017).

It is known that diazepam reduced acute MPH-induced hyperlocomotion but at a dose that also impaired spontaneous locomotor activity, indicating a false negative result (Young et al., 2011; Kanazawa et al., 2017). The absence of MPH effect on exploratory behaviors (holepoke and rearing) could be related to MPH effects on NET, difference in the BPM apparatus construction, or an indication that these behaviors are not reproducible all the time. Interestingly, in a meta-analysis of experiments with DAT knockdown mice in BPM, only 1 in 31 experiments did not detect hyperactivity, while this rate increased to 8 out 31 for rearing and 6 out 29 for holepokes (Kwiatkowski et al., 2019).

The strain of mice is another factor that can influence experimental results and needs to be considered. For example, the DAT inhibitor modafinil increased holepokes in 129/SJ mice but not in C57BL/6J mice (Young et al., 2011). DAT knockdown mice that are generated on a C57BL/6J background showed more consistent results than DAT knockdown mice generated on a 129/SvJ background (Kwiatkowski et al., 2019). Thus, the test of different strains of mice in the BPM apparatus to measure manic-like behaviors will increase its external validity (Drude et al., 2021). In the present study, outbred Swiss mice exhibited manic-like behaviors (hyperactivity and center activity) induced by acute MPH, which extends previous results with

C57BL/6 and DAT knockdown strains and increases the usefulness of the BPM. However, in these latter models, there is also an increase in exploratory behavior. On the other hand, Swiss mice have the characteristics of easy breeding, great availability, and minimal weight variations between males and females. In this line, only males were evaluated in the present study, which is a limitation for translation. Further studies with females are needed.

CONCLUSION

In conclusion, the present study indicated the good positive and negative predictive validity of acute MPH-induced manic-like behaviors in the BPM. We also showed that Swiss mice treated with MPH can be used in the BPM apparatus for searching new antimanic-like drugs.

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