POSTER
T242

The Novel Antiseizure Therapeutic BHV-7000 Demonstrates Antidepressant and Impulse Control Properties in Preclinical Operant Models

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INTRODUCTION

- Epilepsy is associated with a high burden of comorbidities, which can include depression, anxiety, and impulse control deficiencies[1]
- Complex clinical conditions such as depression, attention-deficit hyperactivity disorder (ADHD), and bipolar disorder can be fractionated into discrete symptom clusters such as low motivation, inattention, and low impulse control, which may be more amenable to translational research and treatment
- Compelling evidence exists for targeting Kv7 potassium channel activation in bipolar disorder and major depressive disorder[2]
- BHV-7000 is a small molecule, selective activator of the Kv7.2/7.3 voltage-gated potassium channel that is in late-stage clinical development for focal epilepsy, generalized epilepsy, and other central nervous system indications[3-7]
  - In preclinical studies, BHV-7000 exhibited potent antiseizure efficacy in the maximal electroshock seizure (MES) model with a wide protective index[3]
  - BHV-7000 was safe and well tolerated in phase 1 studies, without central nervous system adverse effects typical of antiseizure medications[8]

OBJECTIVE

- To investigate the effect of BHV-7000 on motivation in the progressive ratio task and on attention and impulse control in the five-choice task at doses corresponding to efficacious exposures in seizure-based models

METHODS

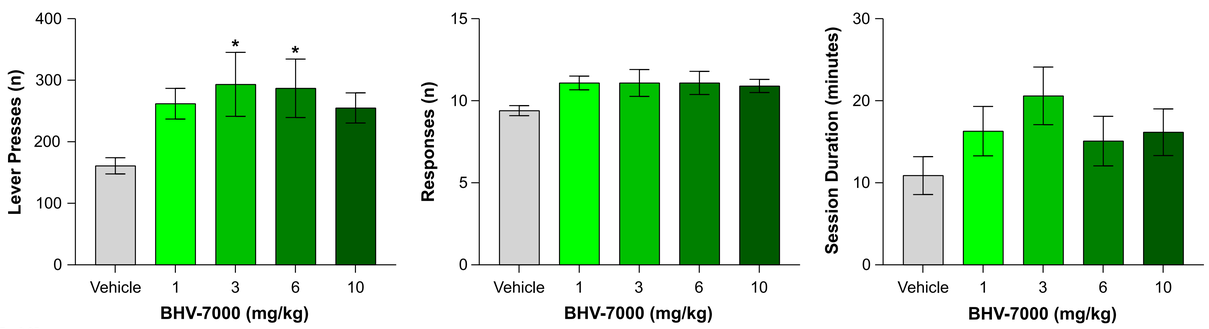
- Male Long Evans rats were trained to either:
  - A progressive ratio (PR) schedule of food reinforcement (N = 40) – a test of motivation, or
  - The five-choice serial-reaction time task (5-CSRTT) – a test of attention and response control (N = 32)
- BHV-7000 was tested at oral doses of 0.3-10 mg/kg
  - This covered a dose range effective against MES-induced seizures in rats[3]
- The PR task required the animal to emit an increasing number of responses in order to obtain consecutive single food reward pellets. At a certain point (ie, the breakpoint), the animal would cease to respond
  - The primary measure was breakpoint; secondary measures of total lever presses and session duration were also recorded
  - Breakpoint was defined as a failure to earn a food pellet within 20 minutes
- For the 5-CSRTT, rats were trained to a final stimulus duration of 0.75s, 5s inter-trial interval (ITI), 5s limited hold, and 100 trials per session. Target performance levels under these conditions were in the range of > 80% accuracy, < 20% omissions. Drug testing began once daily performance levels did not vary by > 15% over 3 consecutive sessions
  - Performance parameters for analysis included percent correct, total trials completed, omissions, correct latency, premature responses, and perseverative responses
- All testing was conducted using a repeated measures design once test subjects had achieved stable baseline performance
- A subgroup analysis was conducted on the low performance tertile subgroups based on total lever presses and breakpoint when dosed with vehicle as a predefined criterion
- Data were reported as means and standard error of the mean, and analyzed by one-way (treatment) or two-way (treatment and performance level for PR; treatment and subgroup for 5-CSRTT) analysis of variants (ANOVA). Significance was set at $P < 0.05$
- All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals

RESULTS

PR Schedule

- BHV-7000 (1-10 mg/kg) produced a nonsignificant trend to increase lever press and breakpoint
- Restricting analysis to the low lever press/breakpoint subgroup (n = 14) revealed a significant main effect of treatment on lever press (F4,52 = 3.2; $P = 0.01$), with this measure significantly increased at the 3 and 6 mg/kg doses relative to vehicle (vehicle: 161 ± 13; 3 mg/kg: 270 ± 25; 6 mg/kg: 293 ± 53) (**Figure 1**)

Figure 1. Progressive Schedule of Food Reinforcement: Low Responder Subgroup (n = 14)

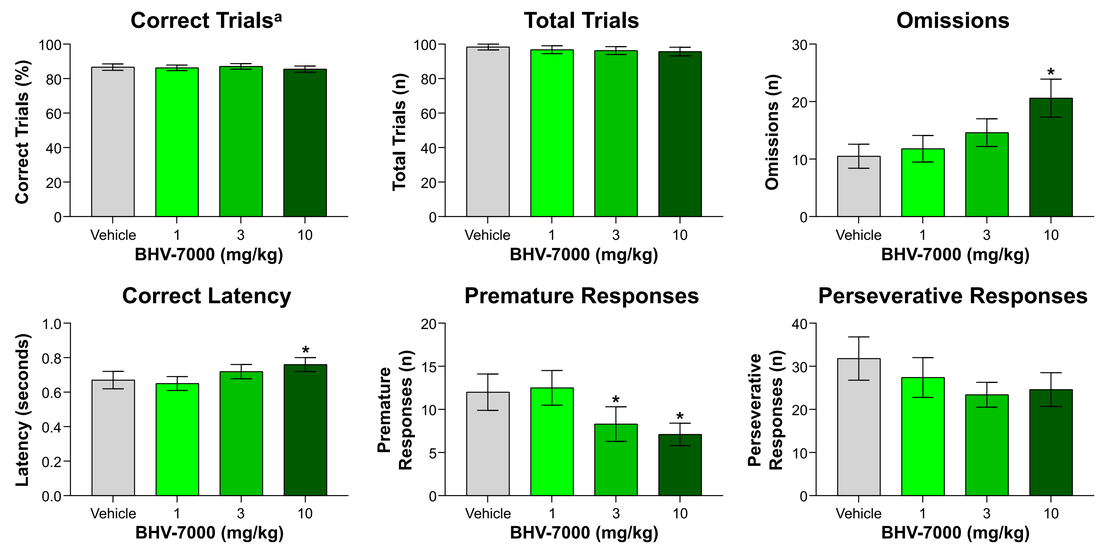


*$P < 0.05$.

5-CSRTT

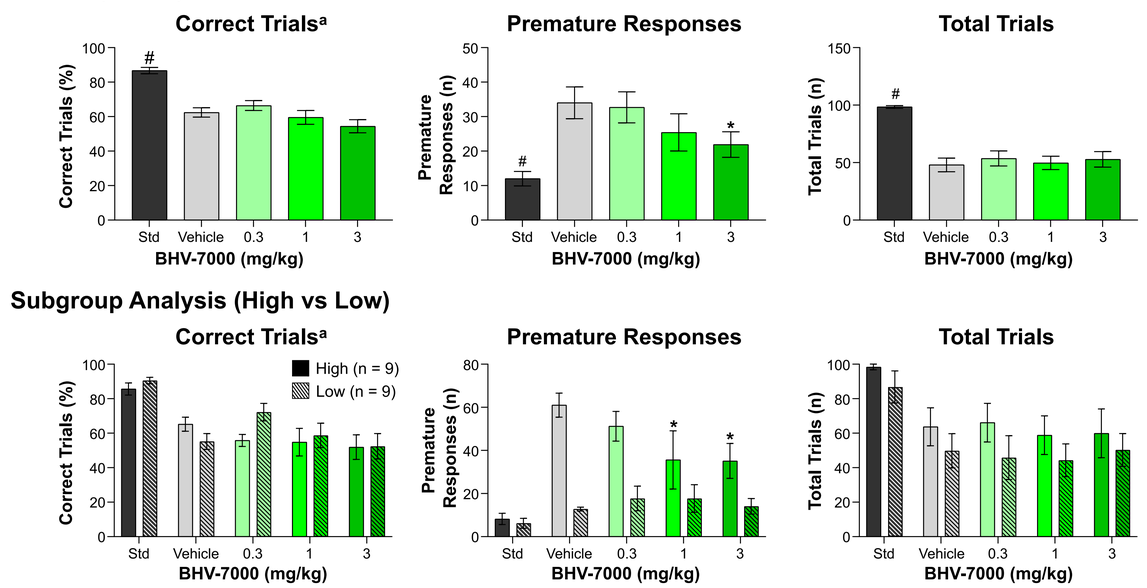
- In rats trained to the 5-CSRTT under standard test conditions, BHV-7000 (1-10 mg/kg) did not detrimentally affect attentional accuracy as measured by the proportion correct (F3,90 = 0.5, nonsignificant) or by total trials (**Figure 2**)
- However, a main effect of treatment was noted on premature responses (F3,93 = 7.0; $P < 0.01$), with BHV-7000 reducing this measure relative to vehicle (vehicle: 23 ± 4; 3 mg/kg: 12 ± 4; $P < 0.01$)
- To investigate further, the ITI was lengthened to 10s to increase the baseline level of premature responses (N = 26; **Figure 3**)
  - Under this test condition, BHV-7000 (1-3 mg/kg) again significantly reduced this measure relative to vehicle pretreatment (vehicle: 61 ± 6; 1 mg/kg: 36 ± 14; $P < 0.05$), without detrimentally affecting the number of trials
  - Premature responses in highly impulsive rats were also reduced without affecting attentional accuracy or trial number

Figure 2. 5-CSRTT: 5s Inter-Test Interval – All Subjects (N = 32)



*$P < 0.05$.
[a]Correct/(correct + incorrect). 5-CSRTT, five-choice serial-reaction time task.

Figure 3. 5-CSRTT: Long, 10s Inter-Test Interval



*$P < 0.05$ vs vehicle. #$P < 0.01$ vs vehicle.
[a]Correct/(correct + incorrect). 5-CSRTT, five-choice serial-reaction time task. Std, standard test conditions (final stimulus duration of 0.75s, 5s inter-trial interval, 5s limited hold, and 100 trials per session).

CONCLUSIONS

- BHV-7000 showed evidence of improving a measure of motivation in low performing rats
- BHV-7000 reduced premature responses in highly impulsive rats, without affecting attentional accuracy or trial number
- Effects were detected at doses (1-6 mg/kg) that overlap with efficacious doses in seizure-based models and were well tolerated in that no detrimental effects on task performance were noted (ie, similar response speed, trials completed, and choice accuracy)
- These results support the potential for BHV-7000 to treat certain comorbidities associated with epilepsy, such as amotivation, a feature of depression, and deficient impulse control, a feature of ADHD and bipolar disorder

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