5-HT_{2C} Agonism: Efficacy in 6-Hz and DBA/2 Mouse Models Supports Utility in Other Epilepsy Syndromes

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Background

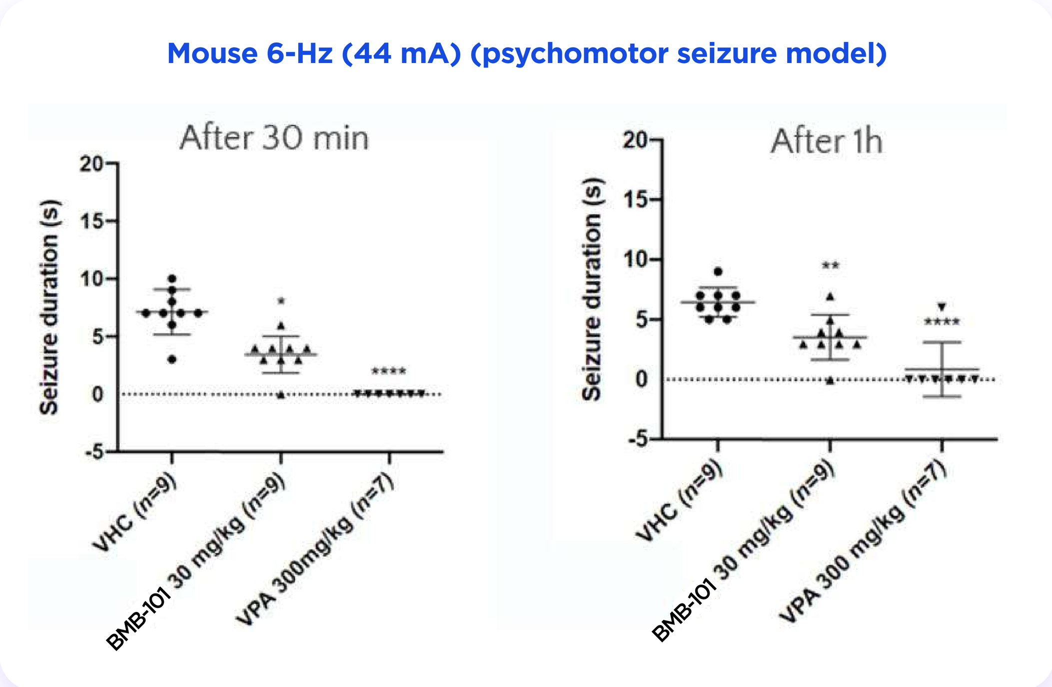
- The 5-HT_{2C} receptor (serotonin 2C receptor), a G protein-coupled receptor (GPCR), has emerged as a potential target for epilepsy treatment due to its role in modulating neurotransmitter release and neuronal excitability
- Traditional 5-HT_{2C} agonists can lead to receptor desensitization, through receptor internalization due to β-arrestin recruitment, reducing long-term efficacy[1]
- The anticonvulsant effects of 5-HT_{2C} receptor activation are primarily mediated in brain regions that include the thalamus, especially the nucleus reticularis thalami, hippocampus, cortex, and associated areas within the cortico-thalamo-cortical network
  - High 5-HT_{2C} receptor expression is found in the hippocampal dentate gyrus, CA1, CA2, and CA3 subfields, as well as the subiculum, where receptor activation suppresses neural network hyperexcitability and inhibits epileptiform activity[2]
- The 6-Hz mouse model of epilepsy is an acute, electrically-induced seizure model used to study pharmaco-resistant partial (focal) seizures[3]
- The DBA/2 mouse model of epilepsy is a genetic animal model characterized by a strong predisposition to audiogenic (sound-evoked) generalized seizures, known as reflex seizures
  - When exposed to high-intensity acoustic stimulation, DBA/2 mice reliably exhibit generalized tonic-clonic seizures that frequently progress to seizure-induced respiratory arrest (S-IRA), cardiac dysfunction, and sudden death, making them a key model for studying both anti-seizure medication effect as well as Sudden Unexpected Death in Epilepsy (SUDEP)[4]

Results

BMB-101 dose-dependently reduces seizure activity in the 6-Hz (44 mA) seizure model

- Seizures are evoked by delivering a 6-Hz electrical stimulus via corneal electrodes, resulting in a distinctive seizure phenotype characterized by momentary stun, vibrissae twitching, forelimb clonus, and Straub tail in rodents.
- This model at high stimulation intensity is particularly sensitive to drugs with novel mechanisms of action, such as levetiracetam, and typically resistant to traditional sodium channel blockers, making it useful for screening new anti-seizure medications for refractory epilepsy
- This model is traditionally run in a low current (22 mA) and in a high current (44 mA) mode, where effect in the 44 mA mode models pharmaco-resistant epilepsy
- Drug-resistant psychomotor seizures were induced 30 minutes to 1 hour after intraperitoneal injection of vehicle (VHC), positive control valproate (VPA), and BMB-101
- In the mouse 6-Hz (44 mA) psychomotor seizure model, BMB-101 significantly reduced the seizure duration at 30 minutes and 1 hour after injection (Figure 1)

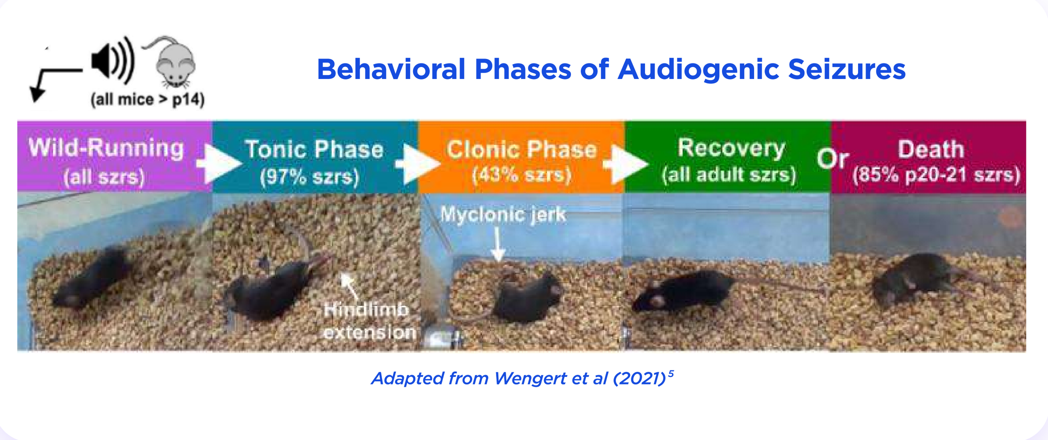
Figure 1. BMB-101 reduces total seizure burden by approximately 50 % in the 6-Hz psychomotor stimulation model at 30 mg/kg



BMB-101 dose-dependently reduces seizure activity in the genetic DBA/2 mouse model

- The DBA/2 mouse line is an inbred mouse line characterized by mutations in Taar1, Asp loci for seizures, Tyrp1 & Gpnmb for glaucoma, and Ltbp4 for muscular dystrophy modifier effects
  - Different mutations define its use in neuropharmacology, epilepsy, glaucoma, and muscular dystrophy research contexts
- As an epilepsy model, seizures are induced through intense auditory stimuli, typically between 100-120 dB
- The number of seizures is age dependent, but experiments are typically conducted between P15 and P49 mice
- Animals were dosed orally at 5, 15, and 30 mg/kg of BMB-101 0.75 hours prior to audiogenic stimulation
- The effect of BMB-101 was scored on stepwise behaviors as illustrated in Figure 2

Figure 2. Genetic DBA/2 Mouse Epilepsy Model



- When the DBA/2 mouse is used as a seizure model, seizures are induced using a loud sound triggered at 100-120 db
- Seizures are then characterized according to phases
- The effect of BMB-101 on individual phases is illustrated in Figure 3

Figure 3a. BMB-101 dose dependently reduces seizure severity and completely abolished death in the DBA/2 mouse model

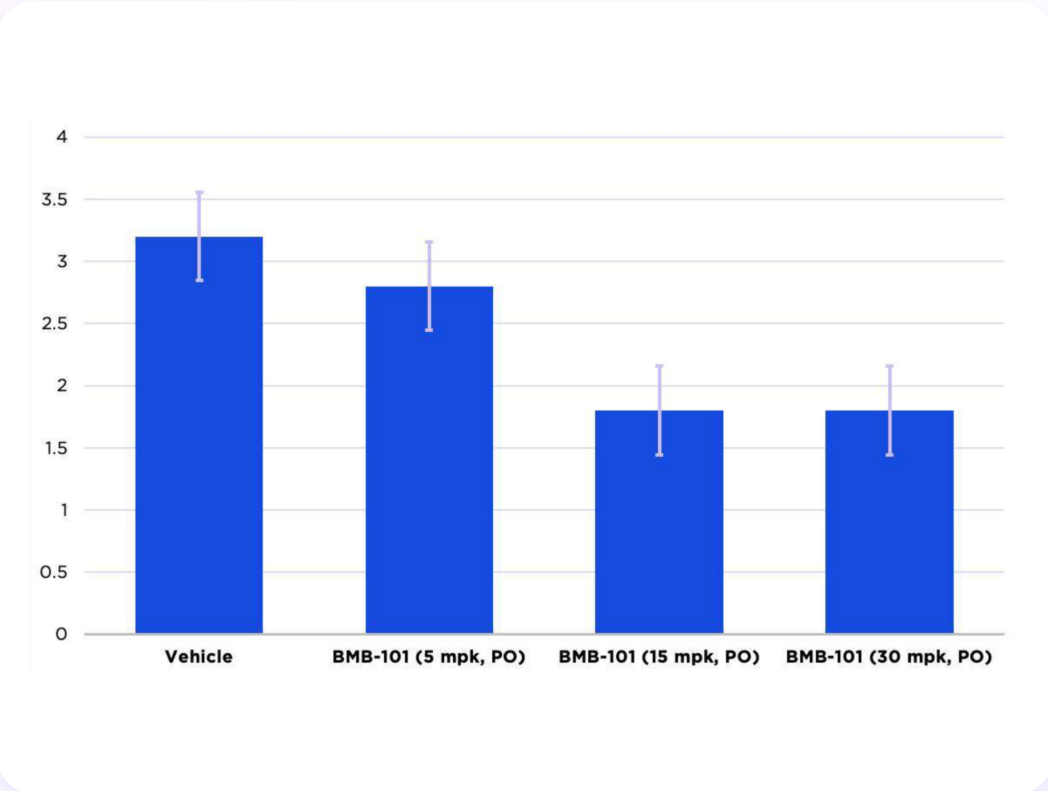
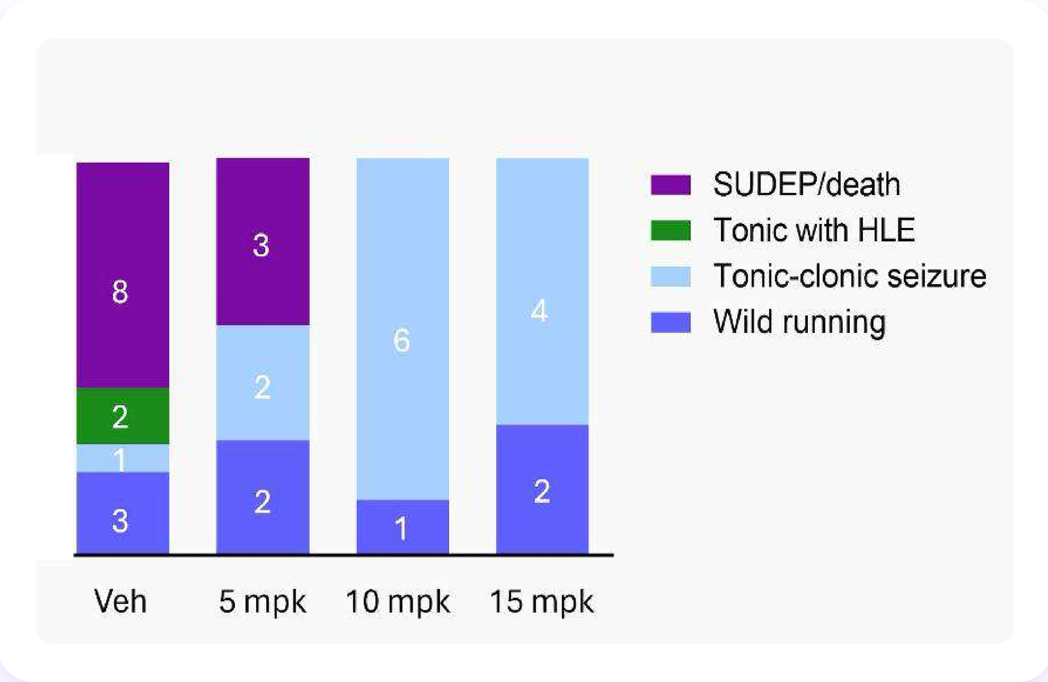


Figure 3b. BMB-101 completely abolished SUDEP and drop attacks in the DBA/2 mouse model



Conclusions

- BMB-101 potently reduced seizures and seizure severity in 2 naturalistic models of seizure activity
- Efficacy in the 6-Hz psychomotor stimulation model suggests that BMB-101 may also have utility in the treatment of refractory focal seizures
- The effect seen in the DBA/2 mouse model may suggest that the use of BMB-101 can influence SUDEP and generalized seizures such as "drop-attacks"- atonic seizures
- The compound's efficacy in animal models is an underestimation due to the following factors:
  - Different selectivity toward rodent 5-HT2 receptors. BMB-101 has reduced efficacy and potency at rodent 5-HT_{2C} receptors.
  - Fast metabolism was demonstrated in rats

References

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