Novel 5-HT2A/2C mixed and partial agonist and its efficacy in preclinical pain models

NINDS satellite forum

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Introduction

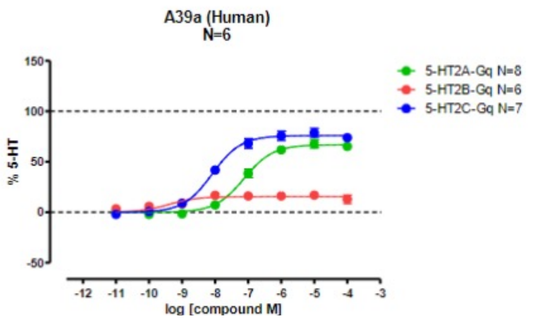
5-HT2A and 2C agonists are emerging as promising candidates for the treatment of pain disorders due to their unique modulation of serotonin pathways, which are closely involved in pain perception and modulation. Activation of 5-HT2A receptors has been shown to enhance analgesic effects by reducing the transmission of pain signals in the central nervous system, potentially offering relief for conditions such as neuropathic pain and fibromyalgia. Similarly, 5-HT2C receptor agonism may contribute to pain management through its role in inhibiting pain signaling and modulating emotional responses associated with chronic pain, thereby improving overall quality of life.
BMB-201 is a novel, selective 5-HT2A/2C agonist discovered by Bright Minds Biosciences that is a candidate for development in neurological and neuropsychiatric indications, including pain. BMB-201 is a prodrug of BMB-A39a which possesses extremely weak 5-HT2B receptor agonism (Emax < 20%), and is not expected to produce hallucinogenic effects due to reduced Emax at 2A receptor

Methods

To test our hypothesis, we employed a combination of in vitro assays, molecular modeling, and preclinical animal models to characterize the receptor binding profile and behavioral effects of BMB-A39a. Preclinical pain models included plantar incision and L5/L6 nerve ligation rat models, where the drug candidate was tested along with morphine and gabapentin as positive controls.

Selective 5-$HT_{2A/2C}$ receptor partial agonist

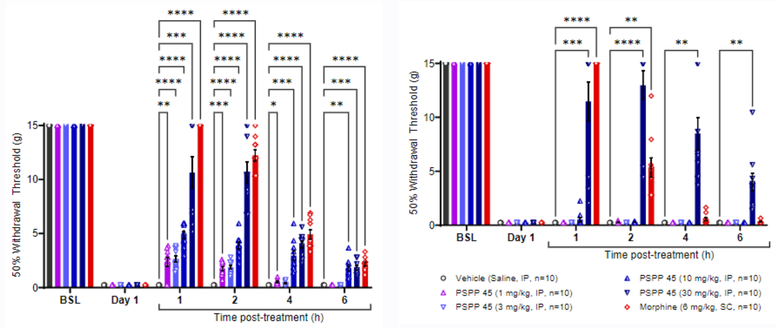
BMB-201's active metabolite, A39a is a partial agonist at 5-HT2A (EC50=70 nM, Emax=69%), 5-HT2C (EC50=6.7 nM, Emax=79%), 5-HT1F (EC50=23 nM, EC50=92%) and 5-HT6 receptors (EC50= 9 nM, Emax=48%). It does not activate other 5-HT receptors.



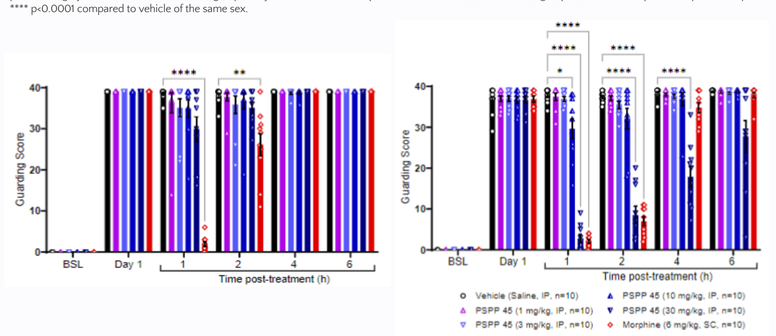
In vitro Pharmacology (John McCorvy group): Effector engagement induced by human 5-HT receptors was measured using Gq dissociation as measured by bioluminescence resonance energy transfer (BRET). Emax was defined relative to serotonin (5-HT).

Plantar incision pain model

This study examined the effects of A39a on mechanical allodynia and guarding behaviors in the plantar incision pain model. In male rats, BMB-201 significantly reduced mechanical allodynia, but not guarding behavior, in a dose-dependent manner. In female rats, 30 mg/kg of A39a significantly reduced both mechanical allodynia and guarding behavior compared to vehicle-treated rats of the same sex. 10 mg/kg also had a modest effect on guarding behavior in females. Morphine was used as a positive control.

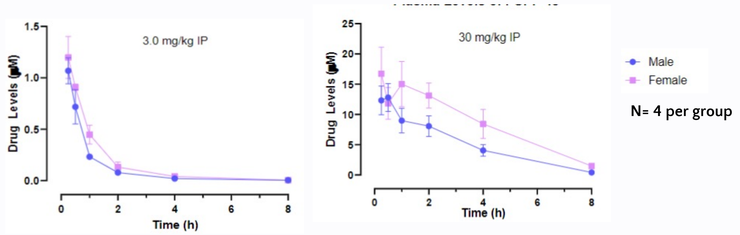


Paw withdrawal thresholds (PWTs) for male (left) and female (right) rats prior to and post-surgery, and 1, 2, 4,and 6 hours post-treatment. PWT for the injured hind paw prior to surgery remained consistent for all groups (Day -1 shown). Data are presented as mean ±SEM, n=10 rats/group.BSL= baseline; *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001 compared to vehicle of the same sex.



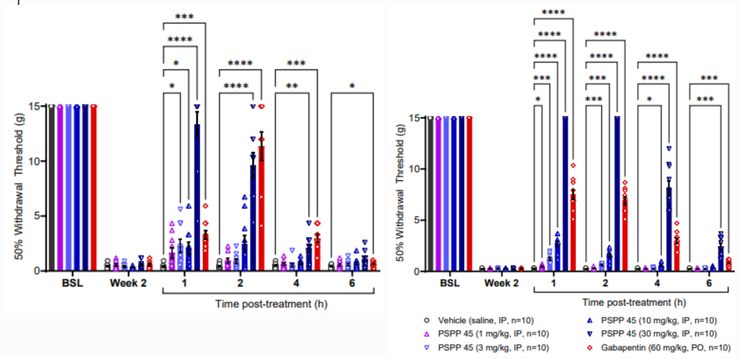
Cumulative guarding scores for male (left) and female (right) rats prior to surgery, post-surgery, and 1, 2, 4, and 6 hours post-treatment. Data are presented as mean ± SEM,n=10 rats/group. BSL=baseline; *p<0.05, ** p<0.01, ***p<0.001, **** p<0.0001 compared to vehicle of the same sex

PK: plasma-concentration after IP dosing

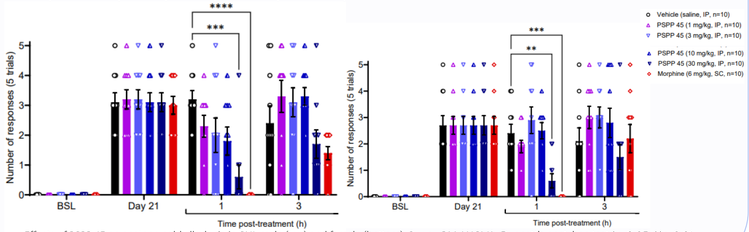


L5/L6 nerve ligation pain model

This study evaluated BMB-A39a on mechanical allodynia in male and female rats 14 days after L5/L6 SNL and on acetone cold allodynia in the same rats 21 days after L5/L6 SNL. Administration of A39a significantly increased PWTs in male and female rats in a dose dependent manner. In both male and female rats, 30 mg/kg significantly reduced the number of acetone responses compared to vehicle-treated rats. Gabapentin and morphine were used as positive controls.



Effects of PSPP 45 on PWT in SNL male (left) and female (right). Only post-op day 14 is shown as all days had consistent responses. 2-way RM ANOVA, with Dunnett's post-hoc test *p<0.05, **p<0.01, ***p<0.001, **** p<0.0001 compared to vehicle of the same sex.



Effects of PSPP 45 on acetone cold allodynia in SNL male (top) and female (bottom). 2-way RM ANOVA, Dunnett's post-hoc test *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to vehicle of the same sex

Conclusions

- This study demonstrates the efficacy of 5-HT2A/2C mixed agonists in preclinical pain model. Reduced Emax (<70%) at 5-HT2A receptor is important to avoid hallucinogenic effects
- This demonstrates the potential of this mechanism in drug development. Clinical trials will be needed to assess the effects in humans

Acknowledgements

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The compound was discovered by Alan Kozikowski group at Bright Minds Biosciences