In vivo characterization of MBDB and its enantiomers in C57BL/6 and autism-like BTBR T+Itpr3tf/J mice

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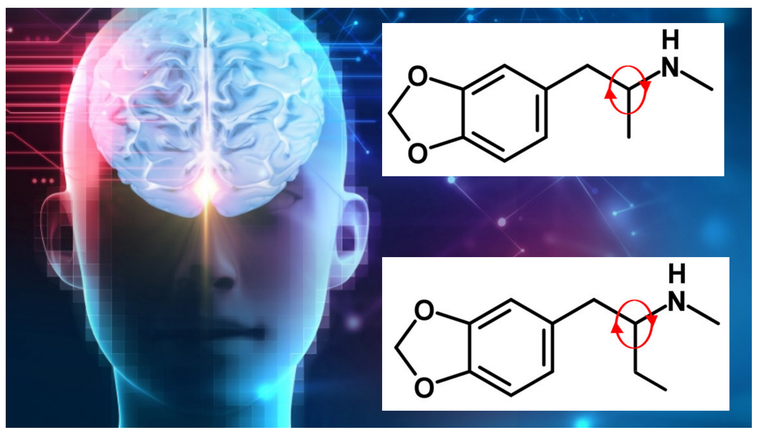
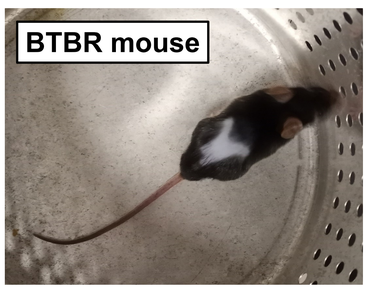
INTRODUCTION



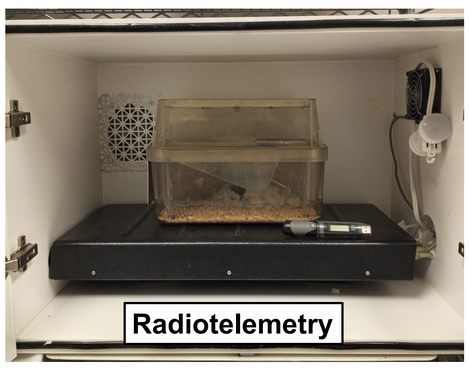
- 3,4-methylenedioxymethamphetamine (MDMA) and related entactogens like 3,4-methylenedioxy-α-ethylamphetamine are being explored as potential treatments for a range of psychiatric conditions.
- MDMA-like entactogens elicit pro-social effects, making them candidates for treatment of social anxiety, but their effects on core temperature, motor activity, and psychedelic-like effects may be treatment-limiting.
- Effects of MDMA, MBDB and their enantiomers have not been adequately studied in autism-like BTBR mice.

ANIMALS



- Adult male BTBR and C57 mice were used.

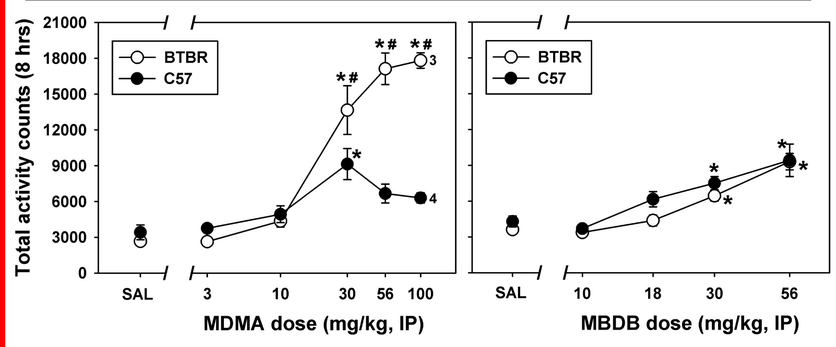
METHODS



- Mice were implanted with indwelling radiotelemetry probes under isoflurane anesthesia.
- Probes streamed movement and core temperature data to a connected computer in 5 min bins.

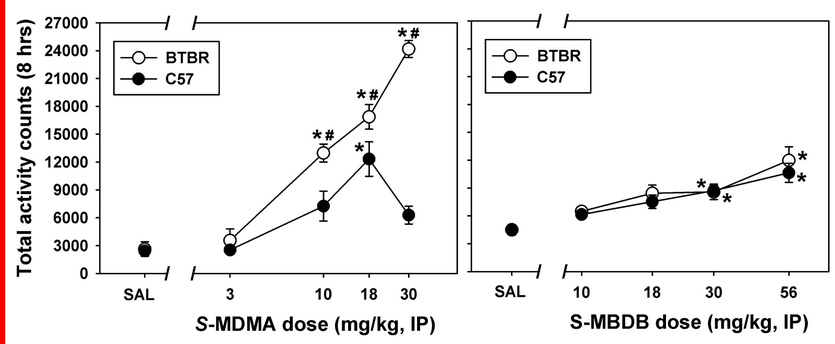
- Mice injected IP with saline or dose of DOI or MBDB.
- After 10 min, mice were placed into observation chambers, video recorded for 10 min, and HTR was later scored by 2 trained observers.

RESULTS – LMA
Racemic mixtures



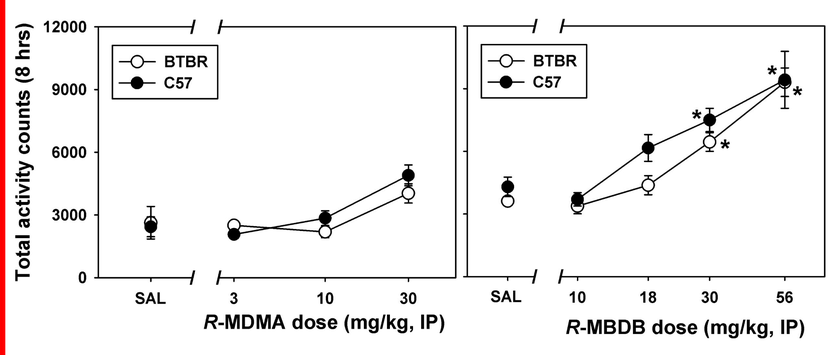
- MDMA and MBDB produced dose-dependent locomotor stimulant effects in both strains.
- BTBRs exhibited greater activity than C57s when treated with MDMA, but not with MBDB.

RESULTS – LMA
S enantiomers



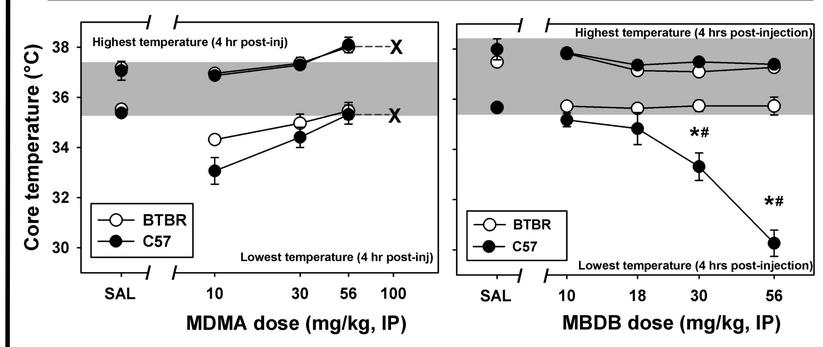
- *S*-MDMA and *S*-MBDB produced dose-dependent locomotor stimulant effects in both strains.
- BTBRs exhibited greater activity than C57s when treated with *S*-MDMA, but not with *S*-MBDB.
- Stimulant effects of *S*-MDMA are greater in magnitude than those of racemic MDMA (note y-axes), but this is not the case for *S*-MBDB vs racemic MBDB.

RESULTS – LMA
R enantiomers



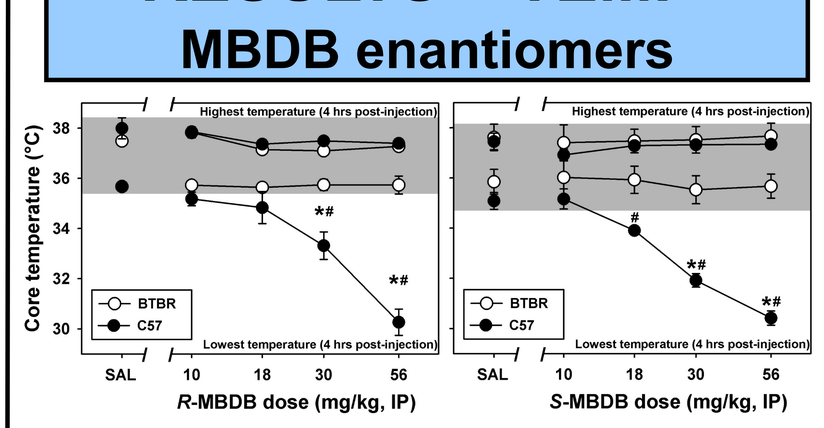
- *R*-MDMA did not significantly alter locomotor activity in either strain, but *R*-MBDB elicited dose-dependent locomotor stimulant effects in both strains.

RESULTS – TEMP
Racemic mixtures



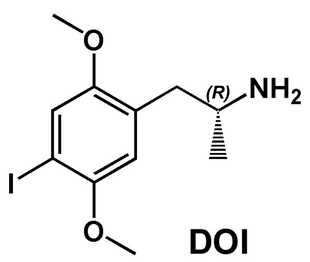
- In both strains, MDMA decreased temperature at small doses and increased temperature at large doses. Lethal effects precluded assessment of max effects at the largest dose.
- MBDB did not alter core temperature in BTBR mice at any dose, but elicited robust dose-dependent hypothermia in C57 mice.

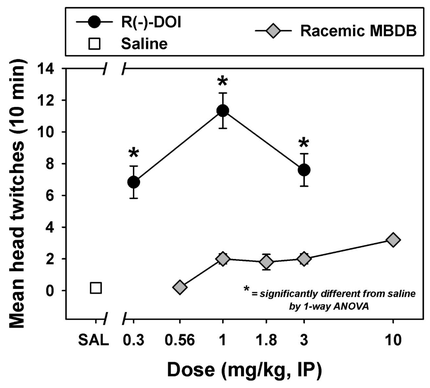
RESULTS – TEMP
MBDB enantiomers



- Effects of S-MDMA were similar to those of racemic MDMA, while R-MDMA elicited hypothermia only (not shown)
- Both MBDB enantiomers elicited robust dose-dependent hypothermia in C57 mice, but did not affect BTBR mice.

RESULTS – HEAD TWITCH





- The classical psychedelic 5-HT2A agonist R(-)-DOI elicited dose-dependent head twitch in C57 mice, but racemic MBDB did not elicit head twitch at any dose.

CONCLUSIONS AND ACKNOWLEDGEMENTS

- Extension of the side chain length from α-methyl in MDMA to α-ethyl in MBDB abolishes the locomotor strain difference between C57s and BTBRs, and eliminates the stereospecificity of effects on core temperature and motor activity.
- These studies illustrate an unusual lack of stereospecificity for the effects of MBDB on locomotor activity in both strains, and on core temperature in C57 mice.
- Further, these studies suggest that it may be possible to separate pro-social effects of MDMA-like drugs from their stimulant-like, hyperthermic, and psychedelic-like effects, at least in the autism-like BTBR mouse.
- Monoamine transporter interactions for MBDB enantiomers should be determined in mouse brain.

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