Thermoregulatory and locomotor effects of 3,4-methylenedioxy-methamphetamine (MDMA), its enantiomers, and a non-racemic mixture of S-MDMA and R-MDMA (ALA-002) in C57BL/6 and BTBR T^{+}Itpr3^{tf}/J mice

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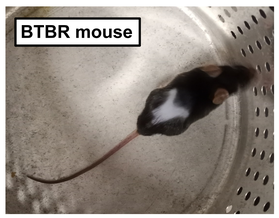
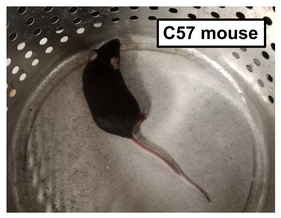
INTRODUCTION

- There is renewed interest in potential therapeutic effects of psychedelic-like drugs such as MDMA.
- MDMA and its analogues are being explored as potential treatments for social withdrawal secondary to Autism spectrum disorder (ASD), but the effects of these drugs in the BTBR T^{+}Itpr3^{tf}/J (BTBR) mouse – the "gold standard" model for ASD research – have not previously been characterized.
- Hyperthermic and locomotor stimulant effects of MDMA have been demonstrated in multiple species, and these effects may be treatment-limiting in a therapeutic context. Non-racemic R/S-MDMA formulations may have reduced thermoregulatory and stimulant effects.

METHODS

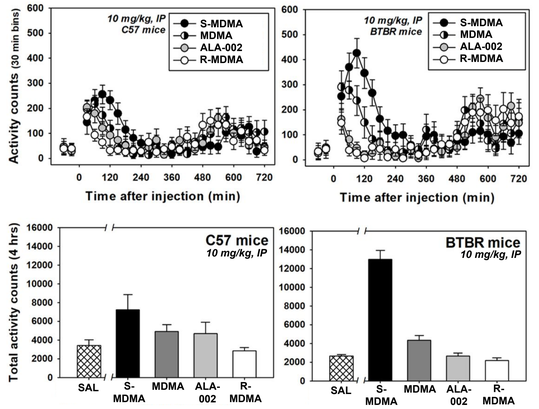
- Mice were implanted with radiotelemetry probes that simultaneously measured core temperature and locomotor activity within the home cage environment.



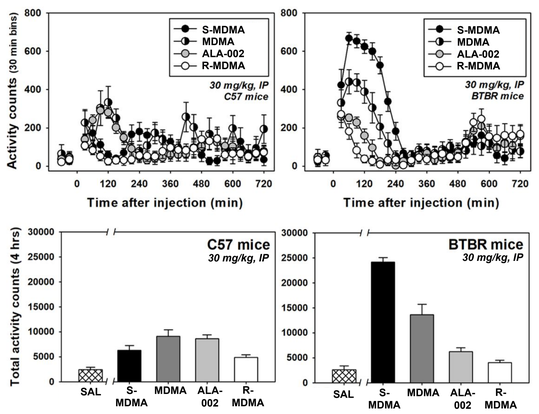


- Mice were injected (IP) with racemic MDMA, S-MDMA, R-MDMA or the non-racemic mixture ALA-002 at a constant volume of 0.01 ml/g after at least 7 days recovery from surgery.
- Longitudinal design where mice received multiple injections (ascending dose order) with 24 to 48 hours between drug administrations.

Locomotor Activity

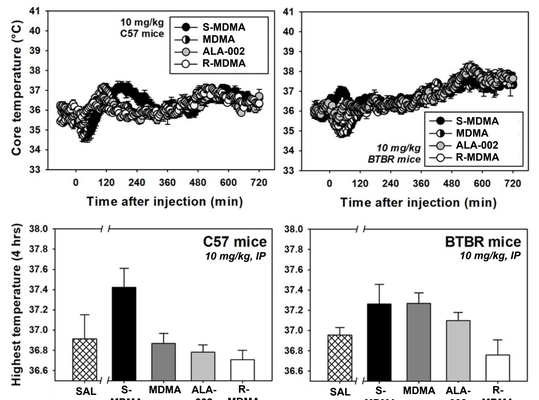


- 10 mg/kg MDMA stimulated locomotor activity depending on its enantiomeric composition, with S-MDMA being more effective than R-MDMA.
- MDMA elicited more motor activity in BTBR mice.

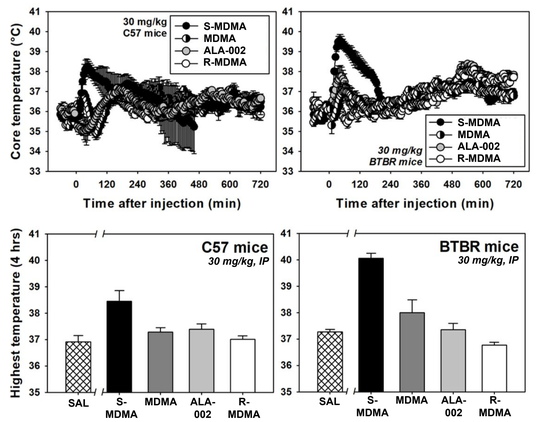


- 30 mg/kg MDMA stimulated locomotor activity depending on its enantiomeric composition, with S-MDMA eliciting stereotypy in C57 mice, but not in BTBR mice.
- MDMA elicited more motor activity in BTBR mice.
- R-MDMA had saline-like effects in both strains, and ALA-002 had saline-like effects in the BTBRs.
- Locomotor effects of MDMA are driven by the presence of the S-MDMA enantiomer.
- Reducing the presence of S-MDMA in enantiomeric mixtures elicits a concomitant reduction in locomotor stimulant effects.

Thermoregulation

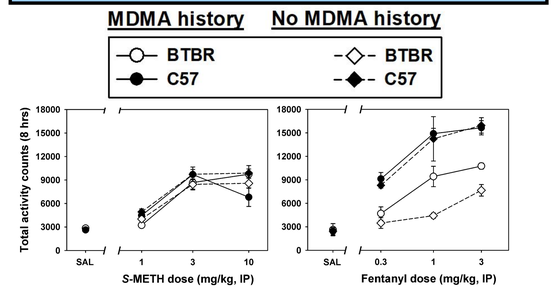


- 10 mg/kg MDMA disrupted thermoregulation depending on its enantiomeric composition, with S-MDMA being more effective than R-MDMA.
- No strain differences were apparent at this dose.



- 30 mg/kg S-MDMA increased core temperature in both strains, but the magnitude of this effect was greater in BTBR mice than in C57s.
- R-MDMA and ALA-002 had saline-like effects in both mouse strains.
- Hyperthermic effects are driven by the presence of the S-MDMA enantiomer.
- Reducing the presence of S-MDMA in enantiomeric mixtures attenuates hyperthermic effects in both mouse strains.

METH and Fentanyl



- BTBR mice are not more sensitive to locomotor effects of ***all*** drugs, but a history of MDMA exposure impacts effects of fentanyl (but not METH) in BTBRs.

CONCLUSIONS

- These studies show that various formulations of MDMA elicit locomotor stimulant and hyperthermic effects in mice that are dependent on the presence of the S-enantiomer.
- Importantly, these studies suggest that ALA-002 elicits reduced abuse-related stimulant effects and is devoid of hyperthermic effects.

FUTURE DIRECTIONS

- Few studies have assessed drug effects in BTBR mice. The present results show that drug effects may not be predictable based on findings in the C57 progenitor strain. Effects of drugs from other pharmacological classes on motor activity and thermoregulation should be studied.
- Novel non-racemic formulations of MDMA or MDMA-like entactogens may maintain therapeutic effects with reduced adverse effects.
- Effects of other MDMA-like entactogens should be determined in BTBR and C57 mice.

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