

The MT₁ Melatonin Receptor As A Principal Mediator Of Methamphetamine-Induced Sensitization in C57BL/6

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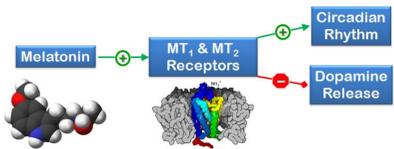
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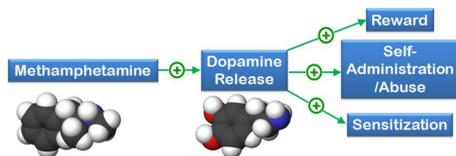


Introduction

- Melatonin is a hormone which mediates circadian time keeping meaning it signals the duration of nighttime to the brain and peripheral tissues of the body.



- Methamphetamine (METH) is a psychostimulant that increases locomotor activity and euphoric sensations in the user.



- Genetic deletion of both MT₁ & MT₂ melatonin receptors abrogates locomotor sensitization in C3H/HeN mice that received 6 repeated METH pretreatments.¹

- Locomotor sensitization is a way to investigate long-lasting neuroadaptations through observing increases in the locomotor activity in magnitude as a result of repeated exposure to a drug of abuse.²

- However 6 repeated METH pretreatments did not induce locomotor sensitization in C57BL/6 mice.

- Previous work reported locomotor sensitization in C57BL/6 mice by a single high dose (5 mg/kg) METH pretreatment³ and by a single cocaine pretreatment.⁴

Goal

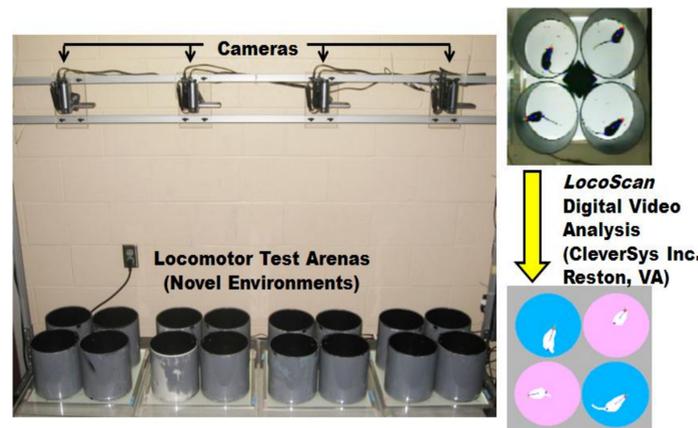
To investigate the role of MT₁ melatonin receptor in locomotor sensitization expressed by C57BL/6 mice after a single METH pretreatment.

References

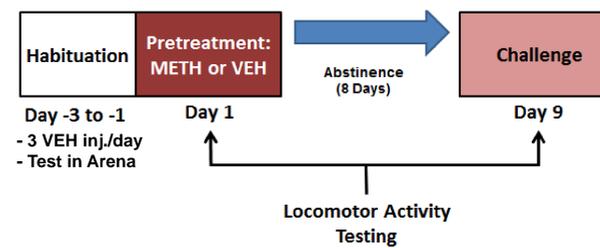
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Supported by NIDA grant
DA021870 (MLD)

Methods



Two Injection Protocol

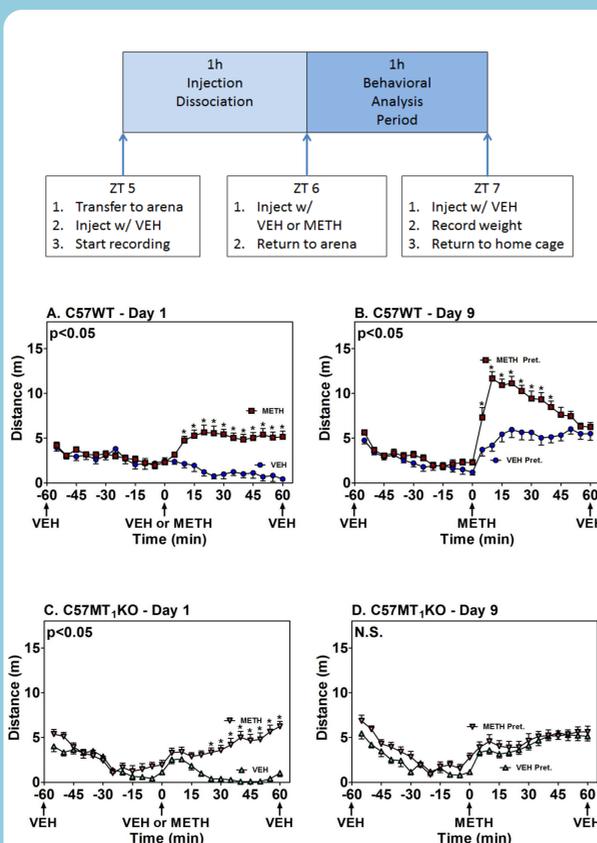


- Locomotor activity data (distance traveled) was collected and analyzed using the **LocoScan** Behavior Analysis System (CleverSys Inc., Reston VA)

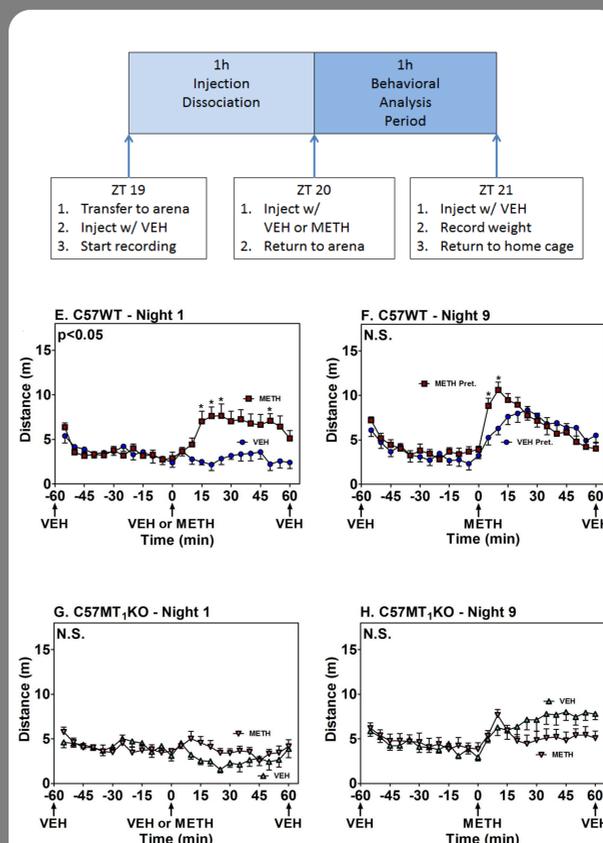
- C57Bl/6 mice:** 6-8 week old males
 - C57WT:** Expresses MT₁ & MT₂ receptors
 - C57MT₁KO:** Genetic deletion of MT₁ receptor
- Tests at **Zeitgeber time (ZT) 5-7** for day experiments and **ZT 19-21** at night (ZT 0 = lights on, 12h:12h light-dark cycle)
- Drugs:**
 - METH (1.2 mg/kg, i.p.)
 - Vehicle (VEH): Saline

Results

Day Experiments (ZT 5-7)



Night Experiments (ZT 19-21)



Summary

- Day Experiments (ZT 5-7)**
 - One METH dose (Day 1) elicits a greater locomotor response than VEH in both WT and MT₁KO.
 - METH challenge triggered a larger locomotor response in METH-pretreated WT mice compared to VEH-pretreated controls; no difference was observed in MT₁KO mice.
- Night Experiments (ZT 19-21)**
 - METH (Night 1) elicits a significant locomotor response *only* in WT mice.
 - METH-pretreated WT mice also expresses locomotor sensitization in the first 15 min after METH challenge (Night 9).
 - Locomotor sensitization is *abrogated* in METH-pretreated MT₁KO mice challenged with METH (Night 9).

Conclusions

- Locomotor sensitization is expressed by C57BL/6 having both MT₁ and MT₂ receptors after a single pretreatment of METH.
- Genetic deletion of MT₁ melatonin receptors *abrogates* locomotor sensitization during day and night in METH-pretreated C57BL/6 mice.
- The MT₁ melatonin receptor regulates the sensitized response to METH and may be a good pharmacological target for drug discovery.