Quinpirole Mediates Aversive Effects of Methamphetamine via Dopamine D2 Receptors

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OBJECTIVE

The objective of this study was to explore the contribution of dopamine D2 receptor to the rewarding and aversive effects of methamphetamine using a genetic mouse model for MA intake.

BACKGROUND

- Methamphetamine (MA) is a highly addictive psychostimulant and its use represents a major burden to public health. Despite this, its mechanism as a psychostimulant is not fully understood and there are no approved medications to assist in treatment[1].
- Risk for MA use is influenced by initial sensitivity to its rewarding and aversive properties[2].
- To induce these effects, MA acts as an indirect agonist on dopamine motivational pathways, which includes dopamine D2 receptors (DR2)[2].
- In a genetic mouse model, mice selectively bred for low MA intake (MALDR) displayed higher sensitivity for aversive properties of MA, whereas mice selectively bred for high MA intake (MAHDR) displayed high sensitivity to the rewarding effects of MA[3]. Furthermore, MA induces hypothermia in MALDR and hyperthermia in MAHDR mice[4].
- Previous pilot studies in our lab have shown that quinpirole, a D2R agonist, can induce hypothermia in MADR mice and their progenitor strains (DBA/2J and C57BL/6J).
- In this study we sought to clarify the role of the D2 receptor in MA motivational effects by testing MADR mice for the rewarding or aversive effects of the D2R agonist, quinpirole, in a condition place preference procedure. We predicted that treatment with quinpirole would induce different levels of hypothermia and different motivational effects in mice with differing innate MA sensitivities.

METHODS

Adult mice (age=111-137 days) from MAHDR and MALDR lines (n=12 per sex per line) were sent from Oregon Health & Science University in Portland, OR to Grand Valley State University (GVSU), Allendale MI. Mice were acclimated for three weeks at the GVSU vivarium before the start of experiment. Following this, mice were subjected to an 18-day conditioned place preference (CPP) procedure (see diagram below) where quinpirole was administered intraperitoneally (IP) at doses of 0.05, 0.1, and 0.5 mg/kg (n=6 per line per sex per dose). For the next two days, thermic responses to vehicle and quinpirole were measured in a random order.

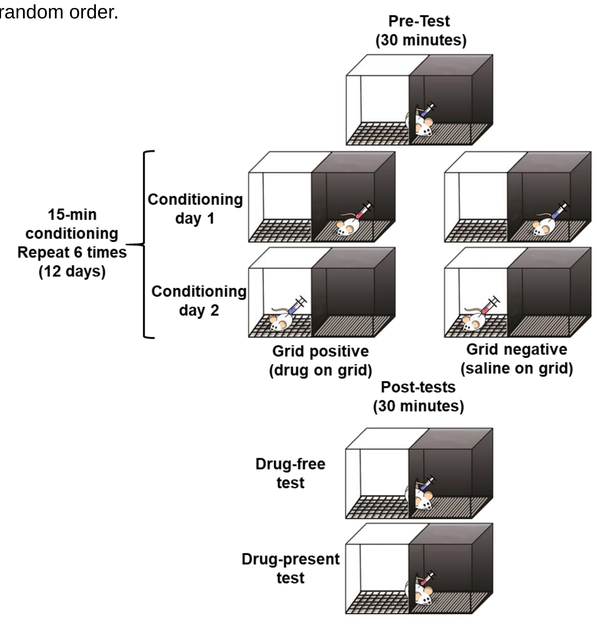

Figure 1. Unbiased condition place preference procedure. A two-compartment CPP apparatus was split by a guillotine door into a left chamber having white wall with a mesh floor and a right chamber having black walls with a grid floor. IR photobeams along the walls detected movement. Mice were given access to both chambers during pre- and post-CPP tests and were restricted to one side during conditioning.

RESULTS

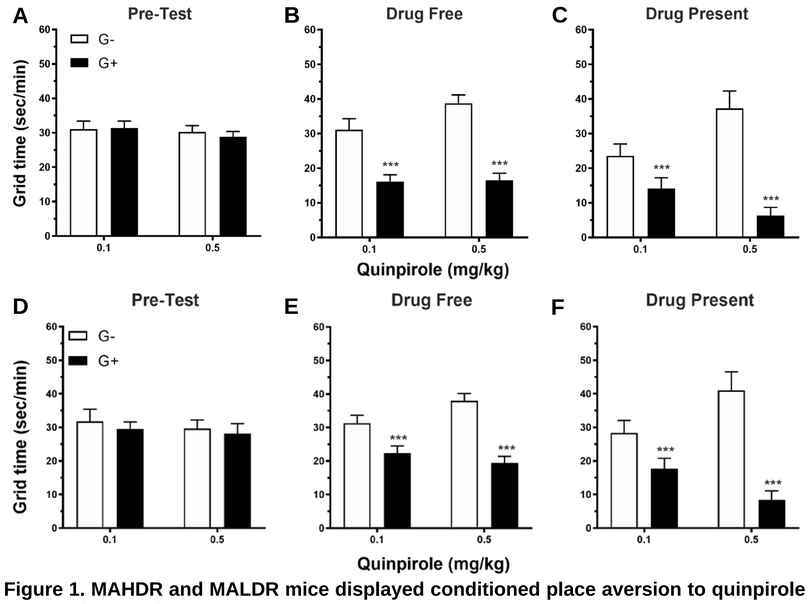

Figure 1. MAHDR and MALDR mice displayed conditioned place aversion to quinpirole at dose 0.1 and 0.5 mg/kg. Shown are mean ± SEM sec/min on the grid floor during the 30-min CPP tests with MAHDR (A-C) and MALDR (D-F) mice. Animals were conditioned with quinpirole with a dose of 0.1 or 0.5 mg/kg on the grid/black (G+) or on the mesh/white (G-) side of the box. ***p<.001 for the difference between G- and G+ mice in the same dose group.

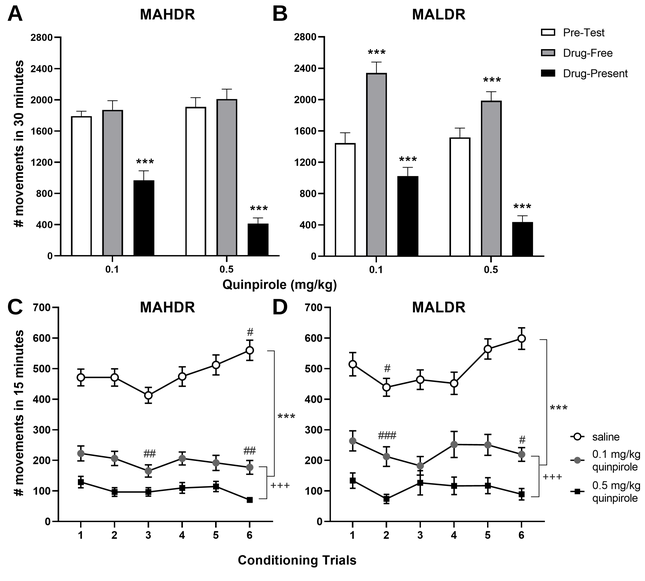

Figure 3. Locomotor activity levels during conditioning and CPP tests in both MAHDR and MALDR were suppressed by quinpirole. Shown are means ± SEM # for movements in a 30 min CPP test (A-B) or in 15 min conditioning trials received quinpirole (C-D). In the pre-test and drug-free test (A-B), mice received saline; in the drug-present test (A-B) they received quinpirole. Conditioning sessions (C-D) were alternated between vehicle and quinpirole in a counterbalanced order. ***p<.001 significant mean difference between the pre-test and other preference test sessions (A-B); ⁺⁺⁺p<.001 significant mean difference between drug-free and drug-present preference tests (B); ***p<.001 significant mean difference between treatments (C-D); +++p<.001 significant mean difference between dose groups (C-D); #p<.05, p<.01, and ###p<.001 significant difference from the first day within a treatment group (C-D).

RESULTS

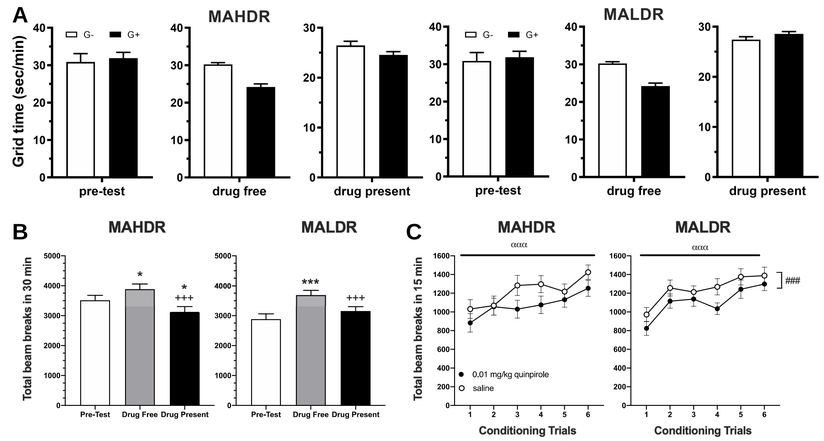

Figure 4. MAHDR and MALDR mice displayed no conditioned place aversion to low quinpirole dose 0.01 mg/kg. (A) Shown are mean ± SEM sec/min on the grid floor during the 30-min CPP tests with MAHDR and MALDR mice. Shown are mean ± SEM total beam breaks, indicating locomotor activity during the 30-min CPP tests (B), and during 15-min conditioning trials (C). *p<.05, ***p<.001 mean difference between pre-test treatment and either drug-free and drug-present tests. ⁺⁺⁺p<.001 mean difference between drug-free and drug-present test day. ###p<.001 mean difference by treatment during conditioning trials in MALDR mice. ᶜᶜᶜᶜp<.001 increase in locomotor activity during conditioning trials.

CONCLUSIONS

- Quinpirole induced significant conditioned place aversion in both lines at modest doses, suggestive that the Drd2 is involved in the aversive properties of MA.
- In mice, administration of modest doses of quinpirole induced significant locomotor suppression, indicative of activation of D2 autoreceptors.
- While locomotor suppression was comparable in the MADR lines, MALDR mice alone demonstrated a compensatory locomotor increase on the drug-free test day. This supports an interaction between the D2R and other genetic risk factors for MA use.
- Low dose of quinpirole induced a modest suppression of locomotor activity compared to saline treatment, only in MALDR mice. In both lines, low dose of quinpirole induced a locomotor sensitization, and a compensatory increase in locomotor activity during the saline (non-drug) days.

FUTURE DIRECTIONS

Future experiments will be aimed at understanding the interaction between dopamine D2 receptor, and trace-associated amine receptor 1 (TAAR1). The TAAR1 is non-functional in MAHDR mice, but functional in MALDR mice[2]. TAAR1 activation also induces CPA, and is thought to share the same transduction pathways with dopamine D2 receptor[2].

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