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Modification of 5-methoxy-*N*,*N*-dimethyltryptamine-induced hyperactivity by monoamine oxidase A inhibitor harmaline in mice and the underlying serotonergic mechanisms

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ABSTRACT

Background: 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) and harmaline are indolealkylamine (IAA) drugs often abused together. Our recent studies have revealed the significant effects of co-administered harmaline, a monoamine oxidase inhibitor (MAOI), on 5-MeO-DMT pharmacokinetics and thermoregulation. This study was to delineate the impact of harmaline and 5-MeO-DMT on home-cage activity in mouse models, as well as the contribution of serotonin (5-HT) receptors.
Methods: Home-cage activities of individual animals were monitored automatically in the home cages following implantation of telemetry transmitters and administration of various doses of IAA drugs and 5-HT receptor antagonists. Area under the effect curve (AUEC) of mouse activity values were calculated by trapezoidal rule.
Results: High dose of harmaline (15 mg/kg, *ip*) alone caused an early-phase (0–45 min) hypoactivity in mice that was fully attenuated by 5-HT_{1A} receptor antagonist WAY-100635, whereas a late-phase (45–180 min) hyperactivity that was reduced by 5-HT_{2A} receptor antagonist MDL-100907. 5-MeO-DMT (10 and 20 mg/kg, *ip*) alone induced biphasic effects, an early-phase (0–45 min) hypoactivity that was completely attenuated by WAY-100635, and a late-phase (45–180 min) hyperactivity that was fully suppressed by MDL-100907. Interestingly, co-administration of MAOI harmaline (2–15 mg/kg) with a subthreshold dose of 5-MeO-DMT (2 mg/kg) induced excessive hyperactivities at late phase (45–180 min) that could be abolished by either WAY-100635 or MDL-100907.
Conclusions: Co-administration of MAOI with 5-MeO-DMT provokes excessive late-phase hyperactivity, which involves the activation of both 5-HT_{1A} and 5-HT_{2A} receptors.

Introduction

Indolealkylamine (IAA) drugs are 5-hydroxytryptamine (5-HT or serotonin) analogs that are able to modulate various physiological and psychological functions including body temperature, attention and behavior [1–3]. Many IAAs are found as psychoactive ingredients of a variety of plant and animal preparations used for medicine, religion and recreation purposes [4–8]. IAAs are also recognized as a major class of drugs of abuse, among which 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT or by the street name "5-MEO") and 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DiPT or "Foxy" and "Foxy methoxy") were placed into Schedule I under the Controlled Substances Act in the United States by Drug Enforcement Administration (DEA) in 2011 and 2004, respectively [9,10]. There are also many reports on IAA intoxications in recent years which include several fatal cases related to the abuse of 5-MeO-DMT or 5-MeO-DiPT [11–19].

5-MeO-DMT is metabolically inactivated by monoamine oxidase A (MAO-A), and thus it is often abused with MAO-A inhibitor (MAOI), *e.g.*, harmaline, to achieve an improved hallucinogenic effect [20]. The pharmacokinetic drug-drug interactions among IAA compounds have been nicely demonstrated using 5-MeO-DMT and MAOI harmaline as model drugs [21–24]. In particular, co-administration of MAOI harmaline leads to a remarkably elevated and prolonged systemic and cerebral exposure to 5-MeO-DMT and an active metabolite bufotenine. In addition, MAOI harmaline greatly increases brain 5-HT levels in mice through the inhibition of 5-HT deamination metabolism [25]. Consequently, 5-MeO-DMT

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pharmacological effects may be significantly altered by co-administered MAOI harmaline [26–29]. Mechanistically, 5-MeO-DMT is rather a relatively less selective 5-HT receptor agonist and it is able to bind to 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors with modest to high affinities [5,30–34]. Due to the presence of consistent pharmacokinetic and pharmacodynamic interactions [2,24], co-administration of 5-MeO-DMT and MAOI may cause hyperserotonergic tone or even serotonin toxicity/syndrome, which exhibits a number of characteristic features in patients and animal models (*e.g.*, neuromuscular excitation such as shivering and tremor, autonomic stimulation such as hyperthermia and tachycardia, and altered mental/behavioral status such as confusion, anxiety, and activity), and has become a more prevalent clinical issue [35–37].

Indeed our recent study has revealed the potentiation of 5-MeO-DMT-induced hyperthermia by MAOI harmaline, and defined the contribution of 5-HT_{1A} and 5-HT_{2A} receptors [28]. In this study, we aimed to delineate the effects of co-administered MAOI harmaline with 5-MeO-DMT on home-cage activities in mice maintained in home cages using an automated telemetry system. In addition, 5-HT_{1A} receptor antagonist WAY-100635 and 5-HT_{2A} receptor antagonists MDL-100907 were utilized to define the serotonergic mechanisms underlying home-cage activities altered by harmaline and 5-MeO-DMT. These results would advance the mechanistic understanding of IAA pharmacological effects on behaviors and the risks of interactions between IAA drugs of abuse.

Material and methods

Chemicals and materials

Harmaline hydrochloride dihydrate, 5-MeO-DMT oxalate, and *N*-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride (WAY-100635) were bought from Sigma–Aldrich (St. Louis, MO, USA). (R)-(+)-(2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]-4-piperidyl]methanol (MDL-100907) was a generous gift from Sanofi-Aventis (Paris, France). Carprofen (Rimadyl) was purchased from Pfizer Inc. (New York, NY, USA). Isoflurane (AErrane) was bought from Baxter Healthcare (Deerfield, IL, USA). All drugs for injection were dissolved in saline and were administered as their free base weights. An injection volume of 10 ml/kg was used for both intraperitoneal (*ip*) and subcutaneous (*sc*) injections.

Animals

All animal procedures were approved by the Institutional Animal Care and Use Committee at University at Buffalo, The State University of New York. Age-matched male FVB/N mice (25–35 g; The Jackson Laboratory, Bar Harbor, ME, USA) were housed in an animal care facility maintained at 20 ± 2.0 °C on a 12-h light/dark cycle (lights on from 6 AM to 6 PM) with *ad libitum* food and water.

Surgical preparations

All the surgery procedures were performed under aseptic conditions as described earlier [28]. A sterile Physiotel TA10TA-F20 telemetry transmitter (Data Sciences International, St. Paul, MN, USA) was implanted into the peritoneal cavity. Mice were anaesthetized with isoflurane in oxygen (4%, reduced as necessary). Carprofen (5 mg/kg) as an analgesic was injected *sc* immediately after surgery and oral (*po*) dosed for 2 more days. After surgery, animals were individually housed for recovery and conditioned for 2 weeks before being used for activity studies in home cages (overall dimensions: mm 365 × 207 × 140 ht).

Experimental procedures

All animals were tested in their home cages in an isolated and quiet room between 10:30 AM and 4:30 PM. On the afternoon before an experimental day, mice were weighted and returned to their home cages, which were placed on individual configured receivers (Data Sciences International, St. Paul, MN, USA). The telemetry transmitter was activated for overnight stabilization and acquisition of baseline activities before experiments. Harmaline (0, 2, 5 or 15 mg/kg; N = 14 mice in each group), 5-MeO-DMT (0, 2, 10 or 20 mg/kg; N = 14 mice in each group) or their combination (0, 2, 5 or 15 mg/kg harmaline plus 2 mg/kg 5-MeO-DMT; N = 11 mice per group) were *ip* administered to the mice. In the combination studies, harmaline was injected 15 min before 5-MeO-DMT treatment. To define the role of 5-HT_{1A} and 5-HT_{2A} receptors in harmaline, 5-MeO-DMT and their combination elicited behavior changes, mice were pretreated *sc* with either 5-HT_{1A} receptor antagonist WAY-100635 (1 mg/kg; N = 7 mice per group) or 5-HT_{2A} receptor antagonist MDL-100907 (1 mg/kg; N = 7 mice in each group). For harmaline (15 mg/kg) treatment, antagonists were dosed 15 min before the administration of harmaline. For 5-MeO-DMT (20 mg/kg) alone and harmaline (2 m/kg) plus 5-MeO-DMT (2 mg/kg) treatments, antagonists were given 15 min before the administration of 5-MeO-DMT. Control animals were given drug vehicle (saline) by following the same injection protocols. After drug administration, the locomotor activities (counts) of individual animals were continuously recorded during the procedures using the same receivers (Data Sciences International, St. Paul, MN, USA), which were controlled by the Ponemah software (Data Sciences International).

Data acquisition and analysis

Mouse home-cage activities (counts) were recorded every 10 s and the average values within a 15 min period were calculated and used for data analysis. Area under the effect curve (AUEC) of home-cage activity values were calculated by trapezoidal method (GraphPad Prism 5, GraphPad Software Inc., San Diego, CA, USA). Because drug-induced changes of animal activities were biphasic, AUEC values were calculated for two periods, an early phase at 0–45 min and late-phase at 45–180 min which better indicated biphasic effects. Depending on the number of groups and variances, data were compared with one-way or two-way ANOVA followed by Bonferroni's *post hoc* tests (GraphPad Prism 5). Difference was considered statistically significant when $p < 0.05$.

Results

High dose of harmaline is able to alter the home-cage activities of mice

Administration of vehicle (0 mg/kg harmaline) introduced some stress to the mice and led to a transient (0–45 min) increase in home-cage activities, which completely returned to the baseline levels later (45–180 min) (Fig. 1A). Compared to the vehicle control treatment, lower doses of harmaline (2 and 5 mg/kg) had no significant effects on mouse home-cage activity (Fig. 1A), which is also indicated by the lack of change in AUEC values (Fig. 1B and C). Interestingly, a higher dose of harmaline (15 mg/kg) significantly reduced the activities of mice at early times (0–45 min) and slightly enhanced the home-cage activities at late phase (45–180 min) (Fig. 1A). The impact of high dose of harmaline on mouse activities is also evidenced by a significant change of $AUEC_{0-45\ min}$ (Fig. 1B) and $AUEC_{45-180\ min}$ values (Fig. 1C).