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Discriminative Stimulus, Rewarding, and Reinforcing Effects of 4-Fluoroethylphenidate in Rodents

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Abstract

Rationale. 4-Fluoroethylphenidate (4F-EPH) is a novel synthetic psychostimulant structurally similar to ethylphenidate, recently detected in illicit drug markets. Its abuse liability remains unclear. **Objectives.** This study aimed to evaluate the abuse-related behavioral effects of 4F-EPH in rodents using various preclinical models. **Methods.** Drug discrimination tests were conducted in male Sprague-Dawley rats trained to differentiate methamphetamine (METH, 0.5 mg/kg) or cocaine (5.6 mg/kg) from saline, and 4F-EPH was subsequently tested for substitution at doses of 1, 2, and 5 mg/kg (i.p.) to assess its interoceptive similarity. Reward potential was assessed in C57BL/6J mice via the conditioned place preference (CPP) test at 1, 10, and 40 mg/kg. Locomotor activity was measured for 60 minutes after 4F-EPH administration (0.01, 0.1, 1, 10, 40 mg/kg). Intravenous self-administration (SA) was used to examine reinforcing effects under a fixed-ratio 1 schedule with 1 or 4 mg/kg/infusion. **Results.** 4F-EPH fully substituted for METH and cocaine with ED_{50} values of 1.655 mg/kg and 2.043 mg/kg, respectively. In CPP, significant place preference was seen at 10 and 40 mg/kg. Locomotor activity increased dose-dependently, peaking at 10 mg/kg. Mice reliably self-administered 1 mg/kg of 4F-EPH; however, the 4 mg/kg dose reduced intake, possibly due to aversive or rate-limiting effects. **Conclusions.** 4F-EPH displays strong METH- and cocaine-like interoceptive effects, rewarding potential, and reinforcing properties, indicating a high abuse potential. Further toxicological evaluation is warranted.

Keywords: 4-Fluoroethylphenidate (4F-EPH), Drug discrimination, Self-administration, Conditioned Place Preference, locomotor-activating, Psychostimulant, Drug abuse potential

Introduction

Synthetic psychostimulants are a diverse class of compounds that exert behavioral effects primarily by increasing the extracellular concentrations of dopamine and other monoamines in the brain(Baumann et al. 2018). Among these, substances structurally related to amphetamine and cocaine have garnered particular attention because of their strong reinforcing effects and high potential for abuse(Marusich et al. 2014; Nagy et al. 2020). The emergence of novel psychoactive substances (NPS), often designed to circumvent legal control while mimicking the effects of established stimulants, continues to pose significant public health and regulatory challenges(Addiction 2020; Schifano et al. 2016; Zawilska 2017).

Fluorinated analogs of ethylphenidate have recently appeared in the illicit drug market, with 4F-EPH being one of the most prominent ones(Corkery and Schifano 2022). Similar to other ethylphenidate derivatives, 4F-EPH is presumed to act primarily as a dopamine reuptake inhibitor, although comprehensive pharmacological characterization remains limited(McLaughlin et al. 2017). Anecdotal reports have suggested that 4F-EPH produces stimulant-like subjective effects similar to those of methylphenidate or cocaine; however, empirical data on its abuse liability are lacking(Corkery and Schifano 2022).

Behavioral pharmacology assays in rodents, such as drug discrimination (DD), conditioned place preference (CPP), locomotor activity, and intravenous self-administration (SA), have proven to be reliable predictors of human abuse potential(Colpaert 1999; Kuhn et al. 2019; Panlilio and Goldberg 2007; Tzschentke 2007). Structurally related compounds, including ethylphenidate and 4-fluoromethylphenidate, produce stimulant-like effects in these models(McLaughlin et al. 2017; Robins et al. 2019). However, the discriminative stimulus properties, reward potential, and reinforcing efficacy of 4F-EPH have not yet been systematically investigated.

Herein, we aimed to evaluate the abuse-related behavioral effects of 4F-EPH using a multi-assay approach in rodents. Specifically, we assessed (1) its ability to substitute METH and cocaine in DD paradigms in rats, (2) its rewarding effects in mice using CPP, (3) its influence on locomotor activity, and (4) its reinforcing potential through SA. These data provide a comprehensive behavioral profile of 4F-EPH and contribute to a growing body of evidence on the abuse liability of novel psychostimulants.

Materials and Methods

Animals

Male Sprague (SD) rats (7–8 weeks old, weighing 180–220 g) and C57BL/6J mice (7 weeks old, weighing 15–20 g) were used. The animals were supplied by the Central Lab. Animal (Seoul, Korea) and Koatech (Busan, Korea). The animals were acclimatized for one week before the experiments. The animals were kept in an environment with a 12-h light/dark cycle, a constant temperature of 23°C, a humidity of 55%, and free access to food and drink. Before the trials, the animals were randomly assigned to treatment groups. The animals were euthanized on the last day of each experiment in accordance with the animal ethical regulations. All animal care, maintenance, and usage procedures were approved by the National Institute of Food and Drug Safety Evaluation/Ministry of Food and Drug Safety Animal Ethics Board (approval number: MFDS-23-021-c2).

Drugs

4F-EPH was synthesized in-house at Kyung Hee University (Seoul, Korea) and dissolved in 0.9% sterile saline. METH hydrochloride and cocaine hydrochloride were obtained from the Sam Eung Industrial Company (Seoul, Korea) and prepared in saline on the day of testing. All drugs were administered via intraperitoneal (i.p.) or intravenous (i.v.) injection as specified.

DD

Male Sprague-Dawley rats (n=10~12 per group) were trained in standard two-lever operant conditioning chambers (Med Associates, St. Albans, VT, USA) to discriminate METH (0.5 mg/kg, i.p.) or cocaine (5.6 mg/kg, i.p.) from saline under a fixed ratio 10 (FR10) schedule of food reinforcement. Daily 15-min sessions were conducted, and training continued until animals reached the criterion of ≥80% drug-appropriate responding across five consecutive sessions. Substitution tests with 4F-EPH (1, 2, and 5 mg/kg, i.p.) were conducted after training. The percentage of drug-appropriate responses and overall response rates (responses/s) were recorded and analyzed.

CPP

The place conditioning apparatus (MED-CPP-3013AT; Med Associates, St. Albans, VT, USA) consisted of three compartments: black, white, and gray (central), separated by guillotine doors. At the beginning of the test, the animals were placed in the central compartment. The black room had a bar grid, and the white room had a mesh grid. The size of the black and white room was 16 × 13 × 12 cm^3. The size of the gray room (central compartment), which was placed between the black and white rooms, was 16 × 13 × 12 cm^3. The illuminance of all the rooms was 12 lx. The time spent in each room was recorded using an infrared sensor. The place preference test was performed as follows: on days 1 and 2, the animals were allowed to move freely in all compartments for 30 min each day for habituation. After measuring the preconditioning for 15 min on day 3, mice with more than a 10% difference in the time spent in one specific room were excluded, and the remaining mice were randomly assigned. On days

4–13, vehicle (saline) or test drugs (METH 1 mg/kg or 4F-EPH (1, 10, and 40 mg/kg), i.p.) were administered on alternate days, and the mice (n = 8 per group) were placed in a specific room for 40 min after the administration of each test drug. Each group of experimental animals was post-conditioned for 15 min, and the time difference between post- and pre-conditioning was calculated.

Locomotor Activity

The locomotor activity test chamber (ENV-520; Med Associates, St. Albans, VT, USA) consisted of a square plastic box (total dimensions: 43 × 43 × 31 cm3) with an infrared beam sensor placed on the floor to measure movement. For habituation, the mice (n = 8 in each group) were allowed to move freely for 1 h in a locomotion test apparatus for 3 days without interference. On day 4 after adaptation, the mice were injected intraperitoneally (0.01, 0.1, 1, 10 and 40 mg/kg), i.p.) with 4F-EPH, and 5 min later, the distance traveled (cm) was recorded for 60 min. The distance traveled was automatically measured using an infrared beam sensor installed on the floor, and the data were recorded using an Activity Monitor SOF-812 (Med Associates).

SA

The SA test was performed in a Skinner box (43 × 43 × 31 cm^3) to conduct operant conditioning experiments with mice. Within this Skinner box, mice respond by obtaining food or drugs as reinforcement using levers (active and inactive levers). The Skinner box was connected to electronic equipment (MED-307A-CT-B1; Med Associates, St. Albans, VT, USA) that recorded the mouse's lever pressing, thus measuring the precise quantification of mouse behavior. A 1 mL syringe containing the drug was placed outside the Skinner box and injected via an infusion pump. Food training was performed for 3 days; on the first day, it was performed overnight in a Skinner box and then continued for an additional 2 days. Mice were trained to press one of the levers for the dispensation of one food pellet (45 mg, Dustless Precision Pellets Rodent, Bio-Serv., Frenchtown, NJ, USA) placed on the food dispenser of the Skinner box and delivered when the mice pressed one of the two levers (active and inactive lever). During the 3 days of food training, food other than that used for food training was limited to 3 g per mouse per day. Only mice whose response score (one response score per lever press) was 90 or higher for 3 consecutive days were selected (a maximum of 100 food pellets per mouse was allowed). Only mice that met the standard test requirements underwent cannulation (infusion pump). The mice were anesthetized with pentobarbital (50 mg/kg, i.p.), and a catheter (26 gauge, PlasticsOne, USA) was inserted into the jugular vein and recovered for 7 days. After cannulation, active lever presses, inactive lever presses, and the number of infusions of 4F-EPH (1 or 4 mg/kg), METH (0.03 mg/kg), or vehicle were measured for 2 h (fixed ratio 1 and time-out 20 s schedule) in mice (n = 8 each group).

Data Analysis

All the data were randomized and analyzed in a blinded manner. All experimental data are represented as mean ± standard error of the mean (SEM), and statistical analysis was performed using GraphPad Prism (GraphPad Software 8, San Diego, CA, USA). Locomotor activity data

were analyzed using a one-way ANOVA followed by Bonferroni post-hoc test. The CPP and SA test data were analyzed using ordinary two-way ANOVA and Bonferroni post-hoc test. *, **, and *** in the figures denote $p < 0.05$, 0.01, and 0.001, respectively.

Results

DD Effects of 4F-EPH in Rats

To evaluate the abuse potential of 4F-EPH, a series of DD experiments was conducted in rats trained to recognize the stimulus effects of METH (0.5 mg/kg) or cocaine (5.6 mg/kg). 4F-EPH produced full substitution (>80% drug-appropriate responding) in rats trained with METH (**Fig. 1a**). The substitution occurred in a dose-dependent manner, reaching 87.7± 10.2% at 5 mg/kg. Similarly, in rats trained with cocaine (**Fig. 2a**), 4F-EPH also induced a high level of substitution, with maximal substitution of 85.6 ± 9.4% at 5 mg/kg, demonstrating comparable interoceptive effects to those of the positive controls. Individual animal data further supported these findings, showing consistent substitution patterns across subjects. Response rates/s were not significantly altered by 4F-EPH in either training group (**Fig. 1b and 2b**), indicating that the observed substitutions did not result from response disruption or sedation. Moreover, the calculated ED_{50} values of 4F-EPH were 1.655 mg/kg in METH-trained rats (**Fig. 3a**) and 2.043 mg/kg in cocaine-trained rats (**Fig. 3b**), suggesting that 4F-EPH is slightly more potent in mimicking METH compared to cocaine. Taken together, these data indicate that 4F-EPH shares strong pharmacological similarity with known psychostimulants and possesses full substitution capability with both METH and cocaine, supporting its high potential for abuse.

Figure 1.

Discriminative stimulus effects of 4F-EPH in rats trained to discriminate METH (0.5 mg/kg, i.p.) from vehicle.

(a) Dose-dependent substitution induced by 4F-EPH, with full substitution (>80%) achieved at 5 mg/kg (87.7 ± 10.2%).

(b) Response rates (responses/sec) following administration of METH and 4F-EPH. Values are expressed as mean ± SEM (n = 10~12).

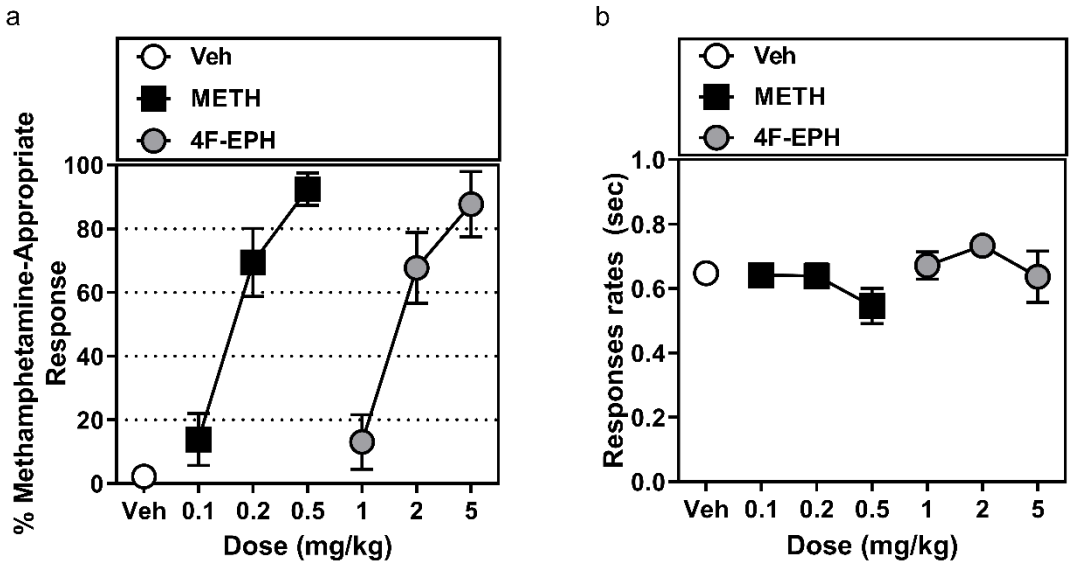


Figure 2.

Discriminative stimulus effects of 4F-EPH in rats trained to discriminate cocaine (5.6 mg/kg, i.p.) from vehicle.

(a) Dose-dependent substitution induced by 4F-EPH, with partial to full substitution observed at 5.6 mg/kg (85.6 ± 9.4%).

(b) Response rates (responses/sec) following administration of cocaine and 4F-EPH. Values are expressed as mean ± SEM (n = 12).

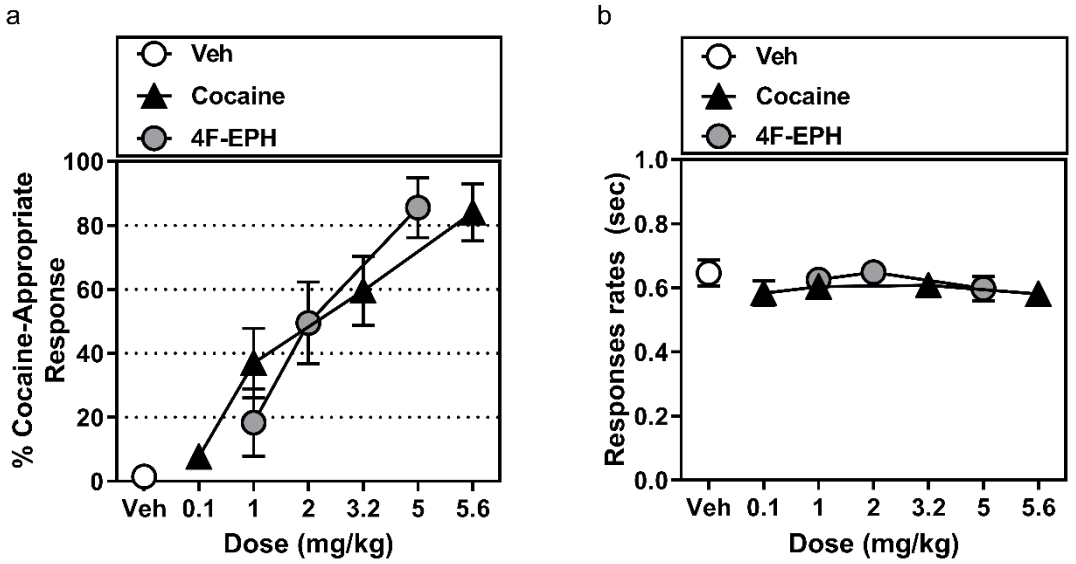


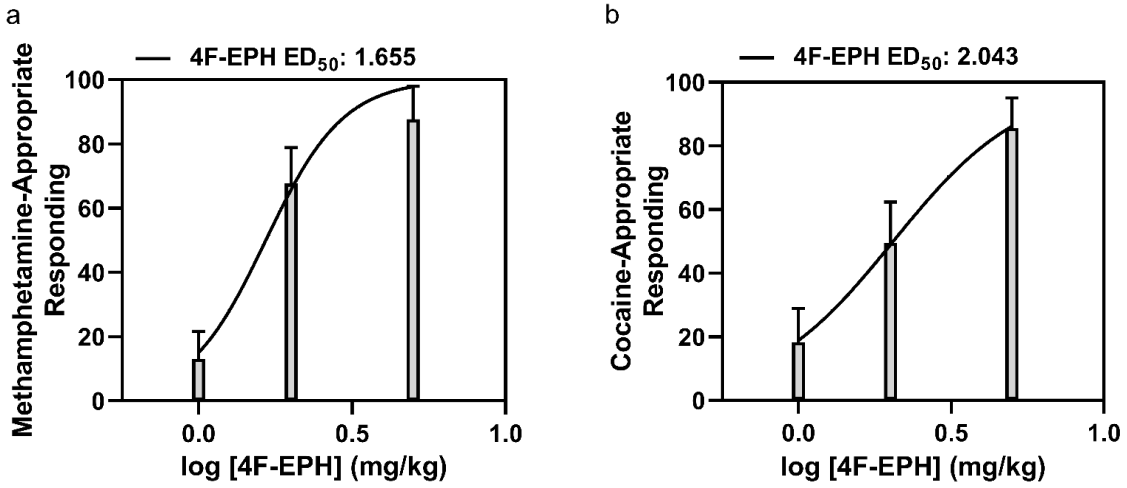
Figure 3.

Comparison of the ED_{50} values for 4F-EPH and positive controls in drug discrimination assays.

(a) ED_{50} for 4F-EPH in METH-trained rats: 1.655 mg/kg.

(b) ED_{50} for 4F-EPH in cocaine-trained rats: 2.043 mg/kg.

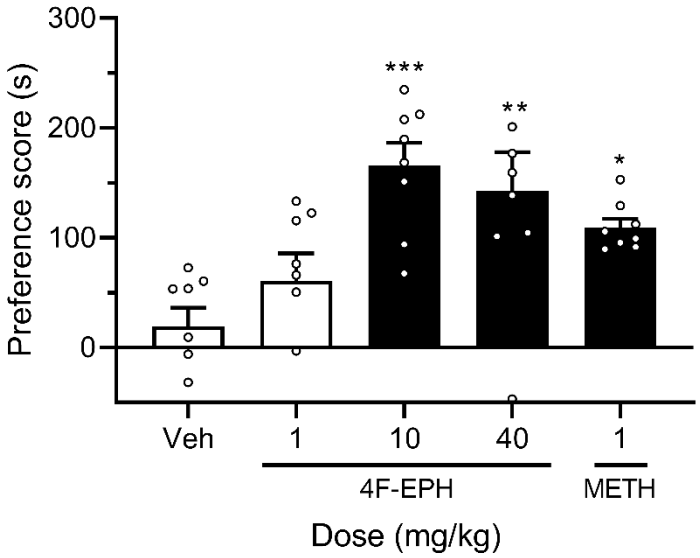
Values are expressed as mean ± SEM (n = 10~12).



Rewarding Effects of 4F-EPH in the CPP Paradigm

The METH (1 mg/kg) group showed the highest place preference (time) compared to other groups. The 4F-EPH (1, 10, and 40 mg/kg) groups showed significant place preference (time) compared to the vehicle group (**Fig. 4**).

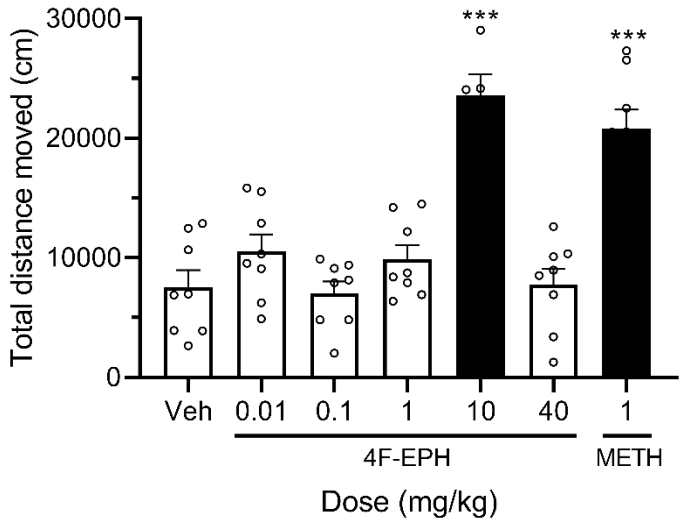
Figure 4. Effect of 4F-EPH administration on the place conditioning paradigm in mice. Time difference spent in the drug-paired and drug-unpaired compartment between the drug administration group and the vehicle (saline) group during pre-conditioning and post-conditioning.Data are expressed as mean ± SEM (n = 8 each group). * $p < 0.05$; ** $p < 0.01$ vs. vehicle, determined by a two-way ANOVA followed by Bonferroni's post-hoc test.



Locomotor-Stimulating Effects of 4F-EPH

The distance traveled (cm) during the 1 h test period, 5 min after drug administration, was greater in the METH and 4F-EPH treatment groups than in the vehicle group. The ambulatory activities of the 4F-EPH (0.01, 0.1, and 1 mg/kg) groups did not differ significantly from those of the vehicle group. In the 4F-EPH 10 mg/kg dose group, locomotor activity significantly increased, and at higher doses (40 mg/kg), locomotor activity decreased (**Fig. 5**).

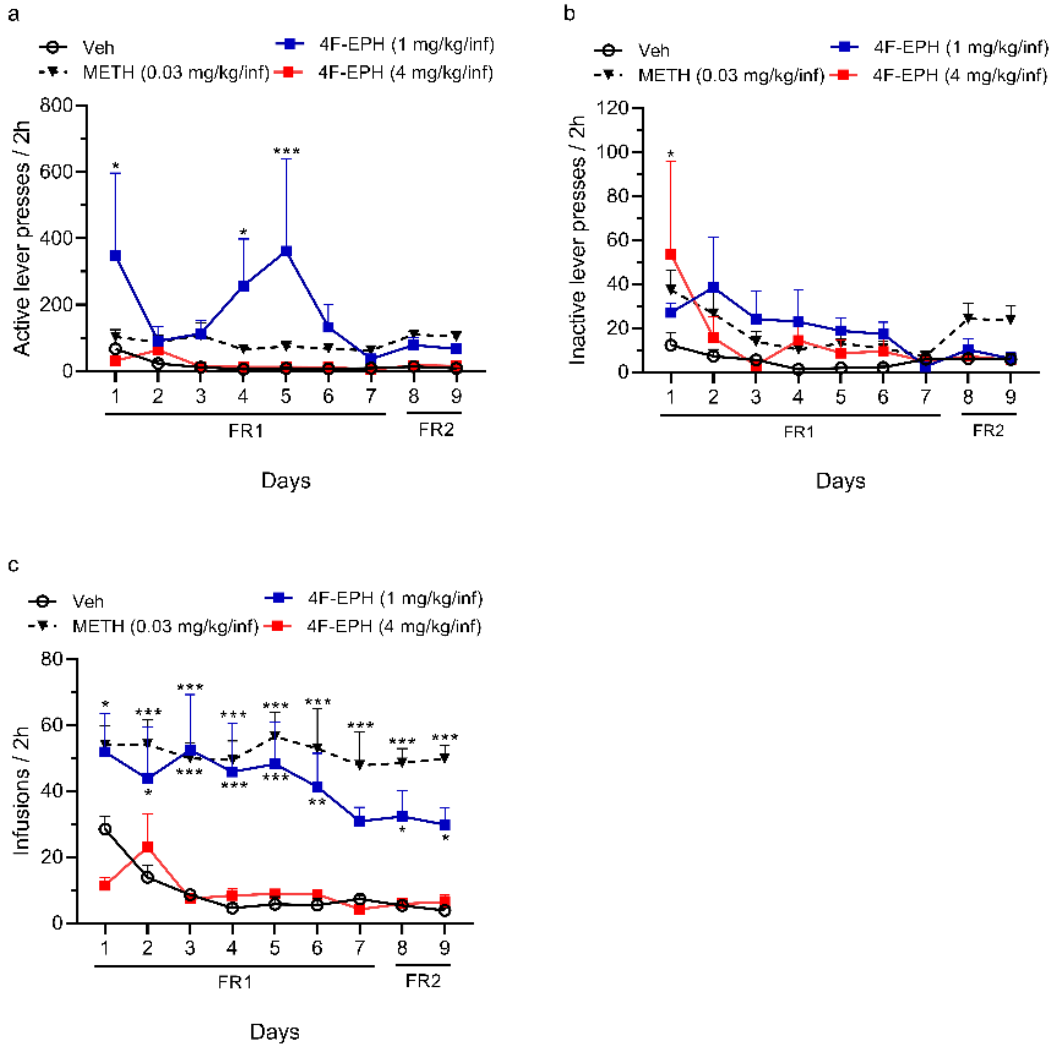
Figure 5. Effect of 4F-EPH administration on the locomotor activity in mice. Mice were administered with vehicle (saline), METH (1 mg/kg), and 4F-EPH (0.01, 0.1, 1, 10, and 40 mg/kg), and the distance traveled (cm) was measured during a 1-h test period. Data are expressed as mean ± SEM (n = 8 each group). *** $p < 0.001$ vs. vehicle, determined by a one-way ANOVA followed by Bonferroni' s post-hoc test.



Reinforcing Effects of 4F-EPH in the SA Paradigm

SA tests were conducted for 2 h/session per day at a fixed ratio of 1 and a time-out schedule of 20 s. Mice with access to METH (0.03 mg/kg/infusion, i.v.) and 4F-EPH (1 mg/kg/infusion, i.v.) exhibited increased activity of lever presses on days 1, 4, and 5 compared to activity exhibited by the vehicle group. Moreover, mice treated with 4F-EPH exhibited significantly increased active lever presses on day 5 (**Fig. 6a**). There was no significant difference in the number of inactive lever presses between groups (**Fig. 6b**). In both the 4F-EPH and METH groups, the number of infusions increased significantly compared with that in the vehicle group (**Fig. 6c**).

Figure 6. Intravenous self-administration (SA) of 4F-EPH and METH. Data are expressed as the mean number of active lever presses (a), inactive lever presses (b), and infusion (c), following SA of 4F-EPH (1 and 4 mg/kg) and METH (0.03 mg/kg). Data are expressed as mean ± SEM (n = 8 each group). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. vehicle, determined by a two-way ANOVA followed by Bonferroni's post-hoc test.



Discussion

This study provides the first comprehensive behavioral characterization of 4F-EPH, a novel synthetic psychostimulant structurally related to ethylphenidate. In multiple preclinical assays, 4F-EPH exhibited METH- and cocaine-like effects, including full substitution for DD, significant CPP, locomotor activation, and intravenous SA. Collectively, these findings suggest that 4F-EPH has significant abuse liability.

In the DD paradigm, 4F-EPH fully substituted for both METH and cocaine in rats, with ED_{50} values within the range of known psychostimulants(McGovern et al. 2014; Mori et al. 2014). DD is a translational model for evaluating the interoceptive effects of psychoactive substances(Colpaert 1987; Huang and Riley 2024), and the ability of 4F-EPH to generalize to both METH and cocaine suggests a psychostimulant-like subjective effect profile.

The CPP results further support the rewarding potential of 4F-EPH. Significant place preference was observed at 10 and 40 mg/kg, comparable to that of METH at 1 mg/kg. CPP is a sensitive measure of drug-associated environmental conditioning that predicts abuse-related effects in humans(Bardo and Bevins 2000; Tzschentke 2000). These findings indicate that 4F-EPH induces robust conditioned reward effects. Consistent with the established predictive validity of CPP, which serves as a sensitive measure of drug-associated environmental conditioning, these results suggest that 4F-EPH may possess abuse-related potential in humans.

Locomotor activation, a hallmark of central dopaminergic stimulation, was also observed in 4F-EPH. The dose-dependent increase in the total distance traveled, peaking at 10 mg/kg, indicated a classic stimulant-like profile(Gatch et al. 2021; Segal and Kuczenski 1997). The attenuated or variable effect at the highest dose (40 mg/kg) may reflect competing behaviors, such as stereotypy or sedation, a phenomenon also seen with high doses of amphetamine derivatives(Heal et al. 2013).

In the SA assays, mice readily self-administered 4F-EPH at 1 mg/kg infusion, with a maintained response across sessions. This is a strong indicator of the reinforcing efficacy and potentially compulsive intake(O'Connor et al. 2011; Panlilio and Goldberg 2007). In contrast, the 4 mg/kg infusion dose resulted in a decreased active lever response, possibly from aversive effects, behavioral suppression, or satiety. Similar dose-dependent patterns have been reported with other potent psychostimulants such as MDPV and α-PVP(Aarde et al. 2013; Gatch et al. 2017).

Taken together, these findings are consistent with the previous behavioral profiles of synthetic stimulants and support the classification of 4F-EPH as a high-risk compound for abuse. The convergence of positive results across multiple paradigms (DD, CPP, locomotor stimulation, and SA) reinforced the potential for human misuse. Moreover, the fact that 4F-EPH was fully substituted by both METH and cocaine suggests a broad interoceptive overlap, thereby

increasing its appeal to users of different stimulant classes.

Given the increasing appearance of 4F-EPH and related compounds in recreational drug markets, early pharmacological assessments are critical for regulatory decisions. Our results provide preclinical evidence that supports scheduling considerations and underscores the need for further studies on the neurochemical and toxicological properties of 4F-EPH.

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Compliance with Ethical Standards
All animal care, maintenance, and experimental procedures were approved by the Animal Ethics Board of the National Institute of Food and Drug Safety Evaluation/Ministry of Food and Drug Safety (approval number: MFDS-23-021-c2). Furthermore, animal care and experimental procedures were conducted in accordance with the ARRIVE guidelines.

Disclosure/Conf lict of Interest
The authors disclose no conflicting interests.

Authors Contribution
MG.K., HK.M., SW.S. and KK.J. conceived and designed the experiments; MG.K. and HK.M. performed the experiments, data collection and analysis, responsible for preparing all animal models and materials; MG.K., HK.M, SW.S., SK.L. and KK.J. drafted, edited, and revised the manuscript. All the authors reviewed drafts of the article and approved the submission of the final draft for publication.

References

Aarde SM, Huang PK, Creehan KM, Dickerson TJ, Taffe MA (2013) The novel recreational drug 3,4-methylenedioxypyrovalerone (MDPV) is a potent psychomotor stimulant: self-administration and locomotor activity in rats. Neuropharmacology 71: 130-40.

Addiction EMCfDaD (2020) New psychoactive substances: global perspective.

Bardo MT, Bevins RA (2000) Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology (Berl) 153: 31-43.

Baumann MH, Walters HM, Niello M, Sitte HH (2018) Neuropharmacology of Synthetic Cathinones. Handb Exp Pharmacol 252: 113-142.

Colpaert FC (1987) Drug Discrimination: Methods of Manipulation, Measurement, and Analysis. In: Bozarth MA (ed) Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer New York, New York, NY, pp 341-372

Colpaert FC (1999) Drug discrimination in neurobiology. Pharmacol Biochem Behav 64: 337-45.

Corkery JM, Schifano F (2022) First Death Involving 4-Fluoroethylphenidate (4F-EPH): Case Report, User Experiences, and Review of the Related Literature. Acad Forensic Pathol 12: 149-166.

Gatch MB, Dolan SB, Forster MJ (2017) Locomotor activity and discriminative stimulus effects of a novel series of synthetic cathinone analogs in mice and rats. Psychopharmacology (Berl) 234: 1237-1245.

Gatch MB, Shetty RA, Sumien N, Forster MJ (2021) Behavioral effects of four novel synthetic cathinone analogs in rodents. Addict Biol 26: e12987.

Heal DJ, Smith SL, Gosden J, Nutt DJ (2013) Amphetamine, past and present--a pharmacological and clinical perspective. J Psychopharmacol 27: 479-96.

Huang S, Riley AL (2024) Drug discrimination learning: Interoceptive stimulus control of behavior and its implications for regulated and dysregulated drug intake. Pharmacol Biochem Behav 244: 173848.

Kuhn BN, Kalivas PW, Bobadilla AC (2019) Understanding Addiction Using Animal Models. Front Behav Neurosci 13: 262.

Marusich JA, Antonazzo KR, Wiley JL, Blough BE, Partilla JS, Baumann MH (2014) Pharmacology of novel synthetic stimulants structurally related to the "bath salts" constituent 3,4-methylenedioxypyrovalerone (MDPV). Neuropharmacology 87: 206-13.

McGovern R, Luderman L, Knecht K, Griffin WC, 3rd (2014) Influence of sensitization on the discriminative stimulus effects of methylphenidate in mice. Behav Pharmacol 25: 766-74.

McLaughlin G, Morris N, Kavanagh PV, Power JD, Dowling G, Twamley B, O'Brien J, Hessman G, Murphy B, Walther D, Partilla JS, Baumann MH, Brandt SD (2017) Analytical characterization and pharmacological evaluation of the new psychoactive substance 4-fluoromethylphenidate (4F-MPH) and differentiation between the (+/-)-threo and (+/-)-erythro diastereomers. Drug Test Anal 9: 347-357.

Mori T, Uzawa N, Kazawa H, Watanabe H, Mochizuki A, Shibasaki M, Yoshizawa K, Higashiyama K, Suzuki T (2014) Differential substitution for the discriminative stimulus effects of 3,4-methylenedioxymethamphetamine and methylphenidate in rats. J Pharmacol Exp Ther 350: 403-11.

Nagy EK, Overby PF, Olive MF (2020) Reinforcing Effects of the Synthetic Cathinone alpha-Pyrrolidinopropiophenone (alpha-PPP) in a Repeated Extended Access Binge Paradigm. Front Psychiatry 11: 862.

O'Connor EC, Chapman K, Butler P, Mead AN (2011) The predictive validity of the rat self-administration model for abuse liability. Neurosci Biobehav Rev 35: 912-38.

Panlilio LV, Goldberg SR (2007) Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction 102: 1863-70.

Robins MT, Blaine AT, Ha JE, Brewster AL, van Rijn RM (2019) Repeated Use of the Psychoactive Substance Ethylphenidate Impacts Neurochemistry and Reward Learning in Adolescent Male and Female Mice. Front Neurosci 13: 124.

Schifano F, Papanti GD, Orsolini L, Corkery JM (2016) Novel psychoactive substances: the pharmacology of stimulants and hallucinogens. Expert Rev Clin Pharmacol 9: 943-54.
Segal DS, Kuczenski R (1997) Repeated binge exposures to amphetamine and methamphetamine: behavioral and neurochemical characterization. J Pharmacol Exp Ther 282: 561-73.
Tzschentke TM (2000) The medial prefrontal cortex as a part of the brain reward system. Amino Acids 19: 211-219.
Tzschentke TM (2007) Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict Biol 12: 227-462.
Zawilska JB (2017) An Expanding World of Novel Psychoactive Substances: Opioids. Front Psychiatry 8: 110.