Preclinical Abuse Liability Assessment of SEP-363856, a Compound with a non-D2 Receptor Mechanism of Action

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Introduction

SEP-363856 is a novel psychotropic agent with a unique, non-D2, non-5-HT_{2A} mechanism of action (MOA) which has shown broad efficacy across multiple animal models relating to aspects of schizophrenia. The molecular targets responsible for the antipsychotic efficacy of SEP-363856 are not fully elucidated but include agonism of trace amine associated receptor-1 (TAAR1) and $5HT_{1A}$ receptors. Based on its unique MOA and profile in animal models, SEP-363856 represents a promising candidate for the treatment of schizophrenia and potentially other neuropsychiatric disorders. Given the central nervous system activity and novel MOA of this new chemical entity and in line with regulatory guidance, a series of preclinical studies were undertaken with SEP-363856 to evaluate potential risk for abuse. A series of abuse-related animal behavioral studies (self-administration and drug discrimination) were conducted in male and female rats to evaluate whether SEP-363856 produces behavioral changes suggestive of human abuse potential. In addition, studies were undertaken to probe the potential for SEP-363856 to block reinstatement of cocaine-seeking behavior in male rats.

Methods

Experimentally naïve rats were housed individually in plastic cages containing bedding. Housing rooms were maintained under a 12/12-hour light/dark cycle at controlled ambient temperature and relative humidity. Animals were allowed to acclimate to laboratory conditions before the beginning of experiments and had free access to water. Access to food was restricted to facilitate training and maintenance of operant behavior with the exception of training of female rats in the MDMA drug discrimination study. Experiments were conducted in operant chambers (MED Associates, Inc., St. Albans, Vermont, U.S.A.) located within sound-attenuating, ventilated cubicles. Each chamber was equipped with a stimulus light, lever(s) located near a food receptacle which was connected to a food pellet dispenser. Chambers used for reinstatement studies were also equipped with a Sonalert® tone generator.

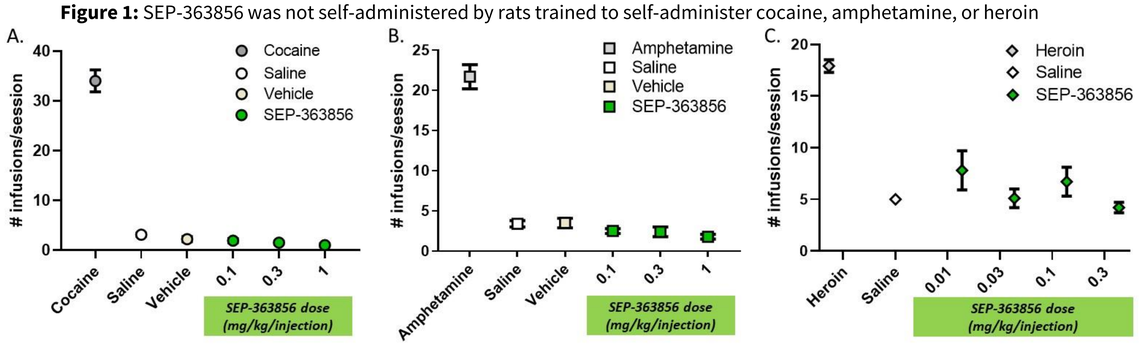
Self-Administration Studies: Following successful completion of operant training and recovery from intravenous (i.v.) catheterization surgery, self-administration training sessions were conducted (0.5 mg/kg/infusion cocaine under an FR10 schedule, 0.07 mg/kg/infusion amphetamine under an FR5 schedule, or 0.015 mg/kg/infusion heroin under an FR3 schedule). After training drug responding stabilized, saline was substituted until self-adminstration was extinguished. Ascending i.v. doses of SEP-363856, selected based on assessment of effects of SEP-363856 on operant behavior, were substituted for training drug for at least 5 consecutive test sessions. Intermittent re-testing with the training drug (0.25 mg/kg/infusion cocaine, 0.07 mg/kg/infusion amphetamine, 0.015 mg/kg/infusion heroin was conducted to ensure maintenance of self-administration behavior. Mean numbers of infusions over the last three sessions of stable responding (or the mean of 10 sessions if there was no stable response) were calculated for each animal.

Drug Discrimination: Following successful completion of operant training, separate groups of rats were trained to discriminate between a training drug (0.6 mg/kg amphetamine i.p. or 1.25 mg/kg 3, 4-methylenedioxymethamphetamine (MDMA) i.p.) and saline in 2-choice lever-pressing tests using food reinforcement (FR10 for amphetamine, FR5 for MDMA). The training substance was administered 15 minutes before the session. When each animal achieved discrimination training criteria, SEP-363856 or buspirone doses were orally administered prior to test sessions. The % of total responses on the training drug-appropriate lever and response rates were calculated for each rat.

Cocaine Reinstatement: After recovery from i.v. catheterization surgery, rats were trained to self-administer cocaine (0.5 mg/kg/infusion) under an FR1, during which each active lever press resulted in infusion delivery as well as a Sonalert® tone sounding, flashing stimulus lights, and extinguishing of the house light for the duration of the infusion. Following successful cocaine self-administration training, extinction sessions were conducted under "prime" or "cue" conditions. During "prime" extinction sessions, cocaine infusions were not delivered; other conditions during extinction were identical to those during self-administration. During "cue" extinction sessions, the house light was illuminated, and the levers were extended but infusions were not administered nor did any other scheduled stimulus change occur. Conditions during reinstatement testing were identical to those during extinction except that an oral dose of SEP-363856 (1-10 mg/kg) or its vehicle was administered 60 min pre-session and a) 17 mg/kg i.p. cocaine was administered 10 min pre-session (i.e., "prime") or b) cocaine self-administered infusions did not occur and cues previously associated with cocaine infusion were presented non-contingently for 6 s at the start of the reinstatement test session (i.e., "cue") and following each right-side lever press. Mean numbers of active lever presses during reinstatement test sessions were calculated for each animal.

Results

Figure 1: SEP-363856 was not self-administered by rats trained to self-administer cocaine, amphetamine, or heroin

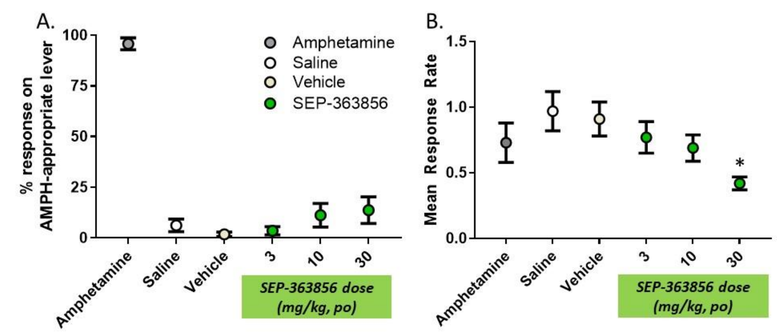


A.) The mean (±SEM) number of infusions in a self-administration (cocaine substitution) test in male SD rats (n=10) was 1.9 ± 0.4, 1.5 ± 0.3 and 1.0 ± 0.3 per session at SEP-363856 dose levels of 0.1, 0.3 and 1 mg/kg/infusion, respectively. The mean number of infusions at each SEP-363856 dose level was significantly lower than the preceding cocaine session mean (range 32.7 ± 2.1 to 33.4 ± 2.7; $p < 0.001$ by Tukey's multiple comparison test) and not significantly different from vehicle (2.2 ± 0.5) or saline (3.1 ± 0.3) controls.

B.) The mean (±SEM) number of infusions in a self-administration (amphetamine substitution) test in male SD rats (n=12) was 2.5 ± 0.3, 2.4 ± 0.6 and 1.8 ± 0.3 per session at SEP-363856 dose levels of 0.1, 0.3 and 1 mg/kg/infusion, respectively. The mean number of infusions at each SEP-363856 dose level was significantly lower than the preceding amphetamine session mean (range 18.5 ± 0.5 to 19.4 ± 0.6; $p < 0.001$ by Tukey's multiple comparison test) and not significantly different from vehicle (3.5 ± 0.6) or saline (3.4 ± 0.4) controls.

C.) The mean (±SEM) number of infusions in a self-administration (heroin substitution) test in male SD rats (n=8-9/session) was 8.0 ± 2.5, 5.4 ± 0.9, 6.4 ± 1.4, and 4.4 ± 0.5 at SEP-363856 dose levels of 0.01, 0.03, 0.1, and 0.3 mg/kg/injection, respectively. The statistically-adjusted mean number of infusions at each SEP-363856 dose level was significantly lower than the heroin acquisition session mean (19.0 ± 0.4, $p < 0.001$ by Dunnett's test) and was not significantly different from the saline extinction session mean (4.8 ± 0.2).

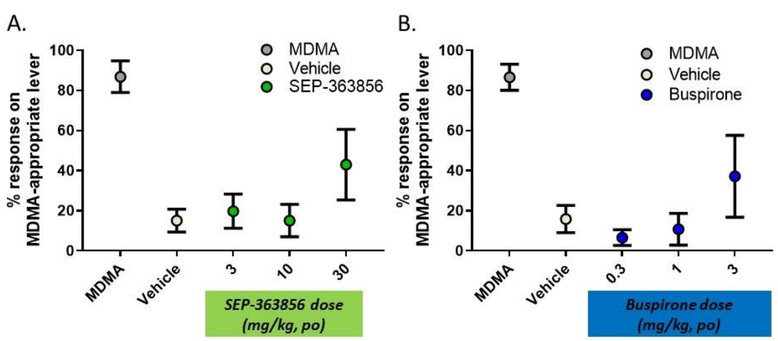
Figure 2: SEP-363856 did not generalize to amphetamine cue in rats



A.) Mean (±SEM) amphetamine-appropriate lever responding of 3.5% (± 2.0%), 11.2% (± 5.8%) and 13.7% (± 6.6%) was observed at 3, 10, and 30 mg/kg SEP-363856, respectively, in male SD rats (n-10).

B.) Mean (±SEM) response rate (response/s) was not affected at 3 and 10 mg/kg SEP-363856 (0.77 ± 0.12 and 0.69 ± 0.10, respectively, versus 0.91 ± 0.13 responses/s with vehicle, $p > 0.05$. At 30 mg/kg, SEP-363856 significantly decreased the response rate (0.42 ± 0.05, *$p < 0.001$ by Tukey's multiple comparison test).

Figure 3: SEP-363856 and buspirone partially generalized to the i.p. MDMA cue in rats



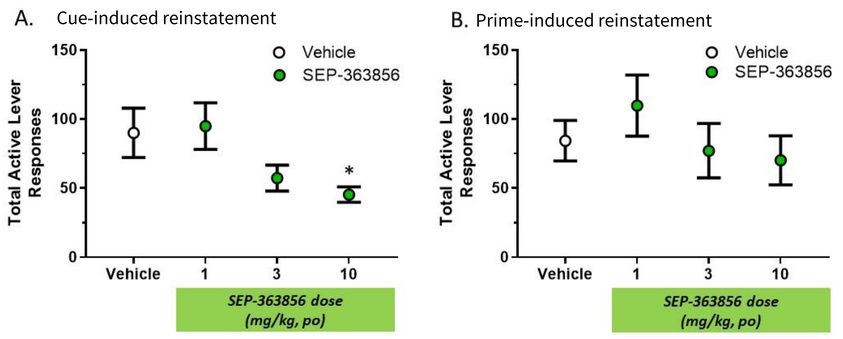
A.) In female Lister hooded rats (n=6-7/dose), SEP-3363856, at 3 an 10 mg/kg, did not generalize to the MDMA cue (19.8 ± 8.5% and 15.1 ± 8.1% generalization to MDMA, respectively). At 30 mg/kg, SEP-363856 partially generalized to the MDMA cue (43.0 ± 17.6% generalization). None of the SEP-363856 doses resulted in unacceptable suppression of lever pressing.

B.) In female Lister hooded rats (n-6/dose), buspirone, at 0.3 and 1 mg/kg, did not generalize to the MDMA cue (6.6 ± 3.9% and 10.8 ± 7.9% generalization to MDMA, respectively). At the highest dose, buspirone partially generalized to the MDMA cue (37.2 ± 20.4% generalization). None of the buspirone doses resulted in unacceptable suppression of lever pressing.

A.) SEP-363856 (10 mg/kg) significantly reduced cue-reinstated responding in male Long-Evans hooded rats (n=11-12/group). Mean (±SEM) numbers of active lever presses during cue-induced reinstatement test sessions were 90.08 ± 17.86, 94.92 ± 16.83, 57.27 ± 9.36, and 45.36 ± 5.55 for vehicle, 1, 3, and 10 mg/kg SEP-363856, respectively (*$p < 0.05$ by uncorrected Fisher's LSD test).

B.) SEP-363856 (1, 3, and 10 mg/kg) did not significantly reduce cocaine prime-reinstated responding in male Long-Evans hooded rats (n=11-12/group). Mean (±SEM) numbers of active lever presses during cocaine prime-induced reinstatement test sessions were 84.38 ± 14.65, 109.82 ± 22.16, 77.08 ± 19.70, and 70.17 ± 17.78 for vehicle, 1, 3, and 10 mg/kg SEP-363856, respectively.

Figure 4: SEP-363856 attenuated cue-induced reinstatement of responding in rats trained to self-administer cocaine (0.5 mg/kg/infusion)



Conclusion: Rats trained to self-administer amphetamine or cocaine did not self-administer SEP-363856. Similarly, SEP-363856 was not positively reinforcing in rats trained to self-administer a low dose of heroin. Based on the established predictive validity of self-administration procedures in rodents, these results suggest the absence of reinforcing effects of SEP-363856 in humans. Over the behaviorally-active dose range of 3 to 30 mg/kg, SEP-363856 did not demonstrate similar subjective qualities to amphetamine in rats trained on an amphetamine cue in a drug discrimination procedure. SEP-363856 and buspirone, a non-scheduled anxiolytic with 5-HT1A partial agonist activity, demonstrated weak (<50%) partial generalization to the cue elicited by MDMA. Collectively, these results suggest that SEP-363856 is not likely to pose a risk for recreational abuse in humans. Further, the reinstatement study results suggest potential therapeutic utility of SEP-363856 in the treatment of substance use disorders which warrants further investigation given the purported role of TAAR1 in addiction.