SEP-363856, a Novel Psychotropic Agent with a Unique, Non-D2 Receptor Mechanism of Action


ABSTRACT

For the past 50 years, the clinical efficacy of antipsychotic medications has relied on blockade of dopamine D2 receptors. Drug development of non-D2 compounds, seeking to avoid the limiting side effects of dopamine receptor blockade, has failed to date to yield new medicines for patients. In this work, we report the discovery of SEP-363856 (SEP-856), a novel psychotropic agent with a unique mechanism of action. SEP-856 was discovered in a medicinal chemistry effort utilizing a high throughput, high content, mouse-behavior phenotyping platform, in combination with in vitro screening, aimed at developing non-D2 (anti-target) compounds that could nevertheless retain efficacy across multiple animal models sensitive to D2-based pharmacological mechanisms. SEP-856 demonstrated broad efficacy in putative rodent models relating to aspects of schizophrenia, including phencyclidine (PCP)-induced hyperactivity, prepulse inhibition, and PCP-induced deficits in social interaction. In addition to its favorable pharmacokinetic properties, lack of D2 receptor occupancy, and the absence of catalepsy, SEP-856’s broad profile was further highlighted by its robust suppression of rapid eye movement sleep in rats. Although the mechanism of action has not been fully elucidated, in vitro and in vivo pharmacology data as well as slice and in vivo electrophysiology recordings suggest that agonism at both trace amine-associated receptor 1 and 5-HT1A receptors is integral to its efficacy. Based on the preclinical data and its unique mechanism of action, SEP-856 is a promising new agent for the treatment of schizophrenia and represents a new pharmaceutical class expected to lack the side effects stemming from blockade of D2 signaling.

SIGNIFICANCE STATEMENT

Since the discovery of chlorpromazine in the 1950s, the clinical efficacy of antipsychotic medications has relied on blockade of dopamine D2 receptors, which is associated with substantial side effects and little to no efficacy in treating the negative and cognitive symptoms of schizophrenia. In this study, we describe the discovery and pharmacology of SEP-363856, a novel psychotropic agent that does not exert its antipsychotic-like effects through direct interaction with D2 receptors. Although the mechanism of action has not been fully elucidated, our data suggest that agonism at both trace amine-associated receptor 1 and 5-HT1A receptors is integral to its efficacy. Based on its unique profile in preclinical species, SEP-363856 represents a promising candidate for the treatment of schizophrenia and potentially other neuropsychiatric disorders.

Introduction

Schizophrenia is a chronic and disabling psychiatric disorder that affects approximately 1% of the global population. It is characterized by positive symptoms (e.g., hallucinations, delusions, and thought disorders), negative symptoms (e.g., flat affect, anhedonia, alogia, and avolition), and cognitive deficits (e.g., impaired memory, attention, and executive functioning). Despite advances in our understanding of the pathophysiology, schizophrenia remains one of the most challenging diseases to treat due to the diversity of clinical symptoms, the heterogeneity of clinical response, the side effects of current treatments, and its association with high morbidity and mortality (Insel, 2010; Meyer-Lindenberg, 2010; Girgis et al., 2019).

Antipsychotics have been the standard of care for schizophrenia since the discovery of chlorpromazine in the 1950s (Charpentier et al., 1952; Laborit et al., 1952; Lehmann and Ban, 1997). Since then, numerous new antipsychotics have been launched, but they have essentially the same mechanism of action, mediating their efficacy against the positive symptoms through antagonism of dopamine D2 and/or serotonin 5-HT2A receptors. Although improvements in drug safety have been made, a focus on the same molecular targets has led to patents related to the subject matter.

At the time these studies were conducted, all authors were employees of Sunovion Pharmaceuticals or PsychoGenics. Some authors are inventors on patents related to the subject matter.

This article has supplemental material available at jpet.aspetjournals.org.

ABBREVIATIONS: CNS, central nervous system; DRN, dorsal raphe nucleus; EEG, electroencephalogram; EPS, extrapyramidal symptoms; FST, forced swim test; KO, knockout; MOA, mechanism of action; PCP, phencyclidine; PPI, prepulse inhibition; REM, rapid eye movement; TAAR1, trace amine-associated receptor 1; Tb, body temperature; VTA, ventral tegmental area.
not led to improved efficacy (Lieberman et al., 2005; Girgis et al., 2019). In fact, the negative and cognitive symptoms remain largely untreated by currently available antipsychotics. Furthermore, approximately 30% of patients have treatment-resistant schizophrenia (Samara et al., 2016). The urgency for new treatments is therefore apparent.

More recently, drug development efforts have focused on molecular targets other than D2 and 5-HT2A receptors, including GlyT1, D4, D6, N-methyl-D-aspartate (NMDA), mGluR2/3, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), 5-HT2c, nicotinic α7, muscarinic M1/M4, H3, NK-3, and σ receptors (Miyamoto et al., 2000; Karam et al., 2010; Girgis et al., 2019). However, despite promising efficacy in preclinical models for many of these targets, most novel, non-D2/5-HT2A mechanism of action. SEP-856 exhibits antipsychotic-like effects through direct modulation of D2 or 5-HT2A receptors.

In this work, we report the discovery of SEP-363856 (SEP-856), a novel psychotropic agent with a unique, non-D2/5-HT2A mechanism of action. SEP-856 exhibits antipsychotic-like efficacy in vivo and demonstrates the potential for treating the positive and negative symptoms of schizophrenia. Although the mechanism of action has not been fully elucidated, in vitro and in vivo pharmacology data suggest that agonism at both trace amine-associated receptor 1 (TAAR1) and 5-HT1A receptors is integral to its efficacy. The data presented in this work suggest that SEP-856 may have broad therapeutic efficacy in schizophrenia and potentially other psychiatric disorders.

Materials and Methods

Animals. Adult male C57BL/6J mice were utilized for behavioral screening, phenocyclidine (PCP)-induced hyperactivity, catalepsy, and prepulse inhibition (PPI) studies, as well as patch-clamp recordings. The forced swim test (FST) was performed in adult male BalbCJ mice. Adult male Sprague-Dawley rats were utilized for electroencephalogram (EEG) recordings, microdialysis, in vivo cellular recordings, autoradiography, and PCP-induced deficits in social interaction.

In vivo assessment of D2 occupancy of SEP-856 was performed in nonhuman primate female baboons (Papio anubis). In vivo pharmacokinetic studies were performed in male adult ICR mice, adult male Sprague-Dawley rats, and male rhesus macaques (Macaca mulatta). Animals were maintained on a 12/12 light/dark cycle. The room temperature was maintained between 20°C and 23°C with a relative humidity maintained between 30% and 70%. Chow and water were provided ad libitum for the duration of the studies, unless otherwise stated. Animals were randomly assigned across treatment groups and studies conducted with experimenters blinded to the drug treatment. Further details (e.g., vendor, age, and/or weight range) are provided in the Supplemental Material.

All animal studies were conducted in accordance with the institutional animal care protocols complying with federal regulations and were approved by the respective Institutional Animal Care and Use Committees.

Test Compounds. Haloperidol, risperidone, quetiapine, clozapine, sertraline, PCP, 8-OH-DPAT, and WAY-100635 were purchased from Sigma-Aldrich. SEP-363856 [(S)-1-(4,7-dihydro-5H-thieno[2,3-c]pyrran-7-yl)-N-methylmethanamine hydrochloride] and its enantiomer SEP-363855 were synthesized by Sunovion Pharmaceuticals, and all doses were corrected for salt content. Further information regarding formulation for each study is provided in the Supplemental Material.

Behavior-Based, Mouse Phenotypic Screening. The central nervous system (CNS) properties of SEP-856 were evaluated using the SmartCube® system, a high-throughput, automated mouse behavioral platform (Roberds et al., 2011; Alexandrov et al., 2015; Shao et al., 2016). Further experimental details are provided in the Supplemental Material.

Behavioral Phenotyping. Details on PPI, PCP-induced hyperactivity, catalepsy, FST, and PCP-induced deficits in social interaction are provided in the Supplemental Material.

EEG Recordings. EEG recordings were performed in seven adult male Sprague-Dawley rats using a crossover design. Animals were implanted with chronic recording devices for continuous recordings of electroencephalograph (EEG), electromyograph, core body temperature (Tb), and locomotor activity via telemetry (DQ ART 4.1 software; Data Sciences, St. Paul, MN). Following completion of the data collection, expert scorers determined states of sleep and wakefulness in 10-second epochs by examining the recordings visually using NeuroScore software (Data Sciences). All doses of SEP-856, caffeine, and vehicle were administered by oral gavage. A minimum of 3 days elapsed between doses. To evaluate the effects of SEP-856 on sleep/wake parameters during the inactive period, dosing occurred during the middle of the rats’ normal inactive period. The first 6 hours of the recording were scored and analyzed. For additional details, please refer to the Supplemental Material.

In Vivo Microdialysis. Extracellular dopamine and serotonin levels were assessed in the prefrontal cortex and dorsal striatum using in vivo microdialysis in freely moving Sprague-Dawley rats. For detailed methods, please refer to the Supplemental Material.

In Vivo Pharmacokinetics Studies. Details on in vivo pharmacokinetic measurements are provided in the Supplemental Material.

In vitro and In Vivo 5-HT1A and D2 Receptor Occupancy Studies. In vitro autoradiography was used to determine the effects of SEP-856 on [3H]-8-OH-DPAT binding to 5-HT1A receptors in rat brain sections. In vivo occupancy of SEP-856 at D2 receptors was measured with [3H]-raclopride in Sprague-Dawley rats and with [3H]-fallypride–positron emission tomography in nonhuman primates (Papio anubis). For details, refer to Supplemental Material.

Patch-Clamp Recordings in the Dorsal Raphe Nucleus and Ventral Tegmental Area. In vitro whole-cell patch-clamp recording techniques were used in isolated slice preparations (male C57BL/6J mice, 4–16 weeks) of the dorsal raphe nucleus (DRN) and ventral tegmental area (VTA) to investigate the effects of SEP-856 on neuronal activity. The experiments examined the effects of SEP-856 (1–30 μM) on the activity of DRN and VTA neurons that were
characterized by their electrophysiological properties and/or their sensitivity to application of the 5-HT_{1A} receptor agonist 8-OH-DPAT (DPAT; 10 µM). Subsequently, effects mediated via the TAAR1 and/or via the 5-HT_{1A} receptor were investigated using the selective antagonist N-(3-Ethoxy-phenyl)-4-pyrrolidin-1-yl-3-trifluoromethyl-benzamide (EPPTB; 0.05–1 µM) and the selective antagonist WAY-100635 (WAY-635; 10 µM), respectively. All compounds were dissolved in either DMSO or ddH_{2}O and diluted with artificial cerebrospinal fluid (aCSF) to a final concentration from a minimum 1000-fold higher stock concentration (maximum slice DMSO concentration 0.1%). Whole-cell patch-clamp recordings were performed at room temperature using the blind version of the patch-clamp technique with either Axopatch 1D or Multiclamp 700B amplifiers. For detailed methods, refer to the Supplemental Material.

**In Vivo Extracellular Single-Unit Recordings in the DRN.**

In vivo extracellular single-unit recordings were used to characterize the effects of SEP-856 on firing of DRN neurons in anesthetized, male Sprague-Dawley rats. Following surgery and insertion of the recording electrode, baseline firing activity of the neuron was recorded for at least 10 minutes prior to the compound administration. SEP-856 was tested at 1, 2, and 5 mg/kg by i.v. injection. After clear inhibitory effects were observed (3–5 minutes after compound administration), WAY-100635 (80 µg/kg, i.v.) was given to determine whether it could antagonize the inhibitory effect of SEP-856. Blood samples were taken 30 minutes following compound administration. For additional details, refer to the Supplemental Material.

**In Vitro Pharmacology.** The in vitro pharmacology of SEP-856 at known receptors and enzymes was assessed in broad panel screens (Eurofins CEREP SA, Celle-Lévescault, France; Ricerca, Taipei, Taiwan). For those targets at which SEP-856 (10 µM) demonstrated greater than 50% inhibition, dose–response curves were generated and inhibitory constant values were determined. Incubation conditions and additional details for equilibrium radioligand binding are listed in the Supplemental Material.

The functional (both agonist and antagonist) effects were also determined. Assays used to study the functional effects were as follows: Intracellular cAMP levels were determined for 5-HT_{1A}, 5-HT_{2A}, TAAR1, and D_{2}, using either the DiscoveRx HitHunter cAMP XS assay or the Cisbio Homogenous Time-Resolved Fluorescence (HTRF) cAMP assay. The 5-HT_{1A} was also studied using GTPγS binding. Impedance was used for 5-HT_{1B}, 5-HT_{1D}, and α_{2A}. Intracellular Ca^{2+} release was used for 5-HT_{2A} and 5-HT_{2C}. Inositol monophosphate (IP\textsubscript{1}) accumulation was used for 5-HT_{2B}. D_{2} was also studied using the DiscoveRx PathHunter β-arrestin recruitment assay.

**Statistical Analyses.** Statistical analyses were performed using the commercially available software GraphPad Prism v6.0, unless otherwise noted. Results are either presented as mean ± S.E.M. or mean ± S.D. (for pharmacokinetics (PK) analyses). Simple comparisons were evaluated with two-tailed, Student’s t test. Multiple group comparisons were assessed with one-way ANOVA, followed by appropriate post hoc analyses. Time-dependent measures were assessed with repeated measures ANOVA followed by appropriate post hoc analyses. Statistical significance was defined as \(P < 0.05\).

**Results**

**SEP-856 Exhibits Antipsychotic-Like Activity in the Smartcube System.** SEP-856 (Fig. 1A) was identified during a medicinal chemistry program designed to develop structurally and mechanistically novel antipsychotics using in vivo mouse phenotypic screening in combination with comprehensive in vitro and in vivo molecular profiling.
Screening was conducted during a 45-minute automated test session, in which mice were exposed to multiple challenges, and different behavioral domains were captured and analyzed using proprietary computer vision software and machine learning algorithms (Roberds et al., 2011; Alexandrov et al., 2015; Shao et al., 2016). The behavioral platform was established and validated with marketed CNS drugs, producing a library of drug-class signatures. Each class is represented by a different color; for example, purple and yellow indicate antipsychotic and anxiolytic-like activity, respectively (Fig. 1E), and the behavioral activity is shown as a scale of 0% to 100%. The data in Fig. 1C demonstrated that SEP-856 was behaviorally active at three of four doses tested (0.3, 1, and 10 mg/kg, i.p.). At 0.3 mg/kg, SEP-856 was classified as an anxiolytic (represented by the primarily yellow color of the column) but showed a dose-dependent increase in antipsychotic classification (purple), such that the signatures at 1 and 10 mg/kg were predominantly antipsychotic-like. As a comparison, the signatures of marketed antipsychotic drugs are shown in Supplemental Fig. 1. In addition, SEP-856 showed a modest antidepressant-like signal, illustrated by the green signal at 0.3, 1, and 10 mg/kg. Overall, the results indicate that SEP-856 is CNS active and exhibits a behavioral signature similar to known antipsychotic drugs. Interestingly, its enantiomer, SEP-363855 (SEP-855), showed little behavioral activity at 10 mg/kg (i.p.), a dose at which SEP-856 was fully efficacious (Fig. 1, B and D).

**In Vitro Pharmacology.** To investigate the molecular targets mediating the response to SEP-856, the compound was tested against several panels of known molecular targets (ion channels, G protein-coupled receptors (GPCRs), and enzymes; Table 1). At 10 μM, SEP-856 showed more than 50% inhibition of specific binding at 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, and 5-HT7 receptors. Inhibitory constant values are shown in Table 1 ranging from 0.031 to 21 μM. SEP-856 showed that SEP-856 exhibited a range of activities at several receptors (Table 2). The most notable activity of SEP-856 was agonism at the human TAAR1 receptor (EC50 of 0.14 ± 0.062 μM, maximum efficacy (Emax) = 101.3% ± 1.3%) and the 5-HT1A receptor (EC50 = 2.3 μM with values ranging from 0.1 to 3 μM, Emax = 74.7% ± 19.6%; Fig. 2B). Interestingly, activity at the human TAAR1 receptor demonstrated stereoselectivity in that SEP-855 (an enantiomer of SEP-856), which was inactive in the behavioral screening platform at 10 mg/kg (i.p.), had an EC50 of 1.7 μM (Fig. 2A). In D2 receptor functional assays, SEP-856 exhibited weak partial agonism with EC50 values of 10.44 ± 4 μM (cAMP, Emax = 23.9% ± 7.6%; Fig. 2C) and 8 μM (β-arrestin recruitment, Emax = 27.1%). At 100 μM, 34% ± 11.6% inhibition was seen in the cAMP assay, and no antagonism was seen at concentrations up to 100 μM in the β-arrestin recruitment assay. Low potency partial agonist activities were also observed at 5-HT2B (EC50 = 15.6 ± 11.6 μM, Emax = 22.4% ± 10.9%), 5-HT3B (EC50 = 0.262 ± 0.09 μM, Emax = 57.1% ± 6.0%), and 5-HT7 receptors (EC50 = 6.7 ± 1.32 μM, Emax = 41.0% ± 9.5%). In a functional assay of 5-HT2B activity, SEP-856 showed no agonism up to a concentration of 10 μM, whereas norfenfluramine, the positive control, was a full agonist with an EC50 value of 0.140 μM. Little to no activity was detected at the 5-HT2A receptor, with 29.3% agonism seen only at the highest tested concentration of 10 μM.

**SEP-856 Exhibits High Brain Penetration and Good Systemic Bioavailability Following Oral Administration.** Behavioral phenotypic screening demonstrated that SEP-856 is CNS active in mice following 0.3, 1, and 10 mg/kg intraperitoneal administration. Consequently, the pharmacokinetics of SEP-856 in plasma was characterized in ICR mice, Sprague-Dawley rats, and rhesus macaques following oral and/or i.v. dosing. Biologic samples were collected over 8 or 24 hours postdose. Brain exposure was also assessed in mice and rats following per os (p.o.) administration. SEP-856 was rapidly absorbed, with maximum plasma and brain concentrations reached within 0.25–0.5 hours in mice and rats and maximum plasma concentrations reached within 6 ± 2.83 hours in monkeys (Supplemental Table 5). SEP-856 penetrated mouse and rat brains after oral administration (10 mg/kg), with average brain-to-plasma area under the curve ratios of approximately 3-4 (Supplemental Fig. 2). In addition, SEP-856 plasma and brain levels were still detectable at 8 hours postdose with fairly consistent brain/plasma ratios over time. SEP-856’s brain penetration and elimination pharmacokinetics as indicated by tmax and half-life were similar to the plasma pharmacokinetics (Supplemental Table 5).

Oral bioavailability of SEP-856, determined by plasma area under the curve ratio after crossover oral and intravenous administrations, was high in rat and monkey with 58% to 120% and ~71%, respectively. Total plasma clearance of SEP-856 was relatively high in rat (5 mg/kg, i.v.) and monkey (5 mg/kg, i.v.) with 1.5 and 0.797 l/h per kilogram, respectively, and elimination half-lives of 1.2 and 3.1 hours, respectively.

**SEP-856 Demonstrates Antipsychotic-Like Efficacy in Rodents.** To demonstrate the antipsychotic-like profile of SEP-856, we performed a series of additional pharmacological studies that assess endophenotypes of schizophrenia and antidepressant efficacy in rodents. Acute treatment with phencyclidine (PCP), which induces robust hyperactivity in rodents and psychosis-like symptoms in humans, is considered a valuable assay in preclinical research and is widely used to screen novel compounds for antipsychotic efficacy (Ratajczak et al., 2013; Steeds

### Table 1

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Kᵢ (μM)</th>
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<tr>
<td>D₂</td>
<td>2.3 ± 8.2</td>
</tr>
<tr>
<td>5-HT₁A</td>
<td>0.284 ± 0.066</td>
</tr>
<tr>
<td>5-HT₁B</td>
<td>1.90 ± 1.72</td>
</tr>
<tr>
<td>5-HT₁D</td>
<td>1.13 ± 0.21</td>
</tr>
<tr>
<td>5-HT₂A</td>
<td>17.25 ± 4.0</td>
</tr>
<tr>
<td>5-HT₂B</td>
<td>1.1</td>
</tr>
<tr>
<td>5-HT₃</td>
<td>2.45 ± 0.82</td>
</tr>
<tr>
<td>5-HT₇</td>
<td>0.031 ± 0.003</td>
</tr>
<tr>
<td>α₂A</td>
<td>0.59 ± 0.06</td>
</tr>
<tr>
<td>α₂B</td>
<td>1.9 ± 0.10</td>
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et al., 2015; Moffat et al., 2017). Single oral administration of SEP-856 (0.3, 1, and 3 mg/kg; 30-minute pretreatment time) resulted in a dose-dependent inhibition of PCP-induced hyperactivity responses in C57BL/6J mice (one-way ANOVA $F(5, 59) = 18.96, P < 0.0001$; Tukey ‘sp o s th o c test, $P < 0.05$) with an ED$_{50}$ of approximately 0.3 mg/kg (Fig. 3A). The positive control, clozapine, also significantly reduced PCP-induced hyperactivity. Small but significant decreases in baseline activity were observed with SEP-856 at the highest dose of 3 mg/kg (one-way ANOVA $F(5, 59) = 5.5, P < 0.001$; Tukey ‘sp o s th o c test, $P < 0.05$; Supplemental Fig. 3A).

Another behavioral assay that is routinely used to identify novel antipsychotic agents is PPI of the acoustic startle response (Geyer et al., 2001). PPI occurs when a startle-eliciting stimulus (i.e., the pulse) is preceded by a stimulus of lower intensity (i.e., the prepulse) and the amplitude of the startle response is reduced. Single oral administration of SEP-856 (0.3, 1, 3, 10, and 30 mg/kg; 30-minute pretreatment time) in C57BL/6J mice resulted in

![Fig. 2. Functional effects of SEP-856 at TAAR1, 5-HT$_{1A}$, and $D_2$ receptors. The functional effects of SEP-856 were determined using HEK-293 cells expressing TAAR1 (A), 5-HT$_{1A}$ (B), or $D_2$ (C) receptors. cAMP accumulation was determined for TAAR1 using the DiscoveRx HitHunter cAMP assay. The inactive enantiomer of SEP-856 (SEP-855) was also tested along with the trace amines phenethylamine (PEA) and p-tyramine. Inhibition of forskolin-stimulated cAMP levels was used for the 5-HT$_{1A}$ ($n = 4$) and $D_2$ receptors; cAMP levels were determined with the DiscoveRx HitHunter cAMP XS assay or the Cisbio HTRF, cAMP assay. The $D_2$ receptor was also studied using the PathHunter $\beta$-arrestin recruitment assay. Representative traces are shown for (A and C).](https://jpet.aspetjournals.org)
a dose-dependent increase in PPI compared with the respective vehicle treatment (Fig. 3B), with significant increases observed at 3, 10, and 30 mg/kg compared with their respective vehicle controls (10% DMSO for haloperidol and 20% cyclodextrin for SEP-856; one-way ANOVA *P < 0.05). Unlike the positive control haloperidol, SEP-856 improved PPI at dose levels that had no confounding effects on baseline startle responses (Supplemental Fig. 3B).

In contrast to positive symptoms, negative symptoms of schizophrenia, including anhedonia, blunted affect, and social withdrawal, are more difficult to model in animals (Jones et al., 2011; Wilson et al., 2015). However, subchronic treatment with PCP reliably produces social interaction deficits in rodents that may mimic certain aspects of negative symptoms such as social withdrawal (Steeds et al., 2015). Sprague-Dawley rats were subcutaneously injected with PCP (2 mg/kg) or vehicle twice daily for 5 days in Sprague-Dawley rats were significantly attenuated by acute clozapine (2.5 mg/kg, i.p.) and SEP-856 (p.o.) treatment at all doses tested (one-way ANOVA *P < 0.05 vs. PCP/Veh, #P < 0.05 vs. Veh/Veh).

The effects of SEP-856 (0.3, 1, 3, and 10 mg/kg) were additionally evaluated in the mouse FST, a behavioral assay...
that is acutely sensitive to all major classes of marketed antidepressive drugs (Porsolt et al., 1977). Single oral administration of SEP-856 significantly reduced immobility time at 1, 3, and 10 mg/kg compared with vehicle (one-way ANOVA F(5, 44) = 13.24, P < 0.0001; Tukey’s post hoc test, P < 0.05; Fig. 3D), suggesting that SEP-856 may also exhibit antidepressive-like activity. However, no clear dosedependent effect was observed, and the magnitude of response was smaller than that produced by the positive control sertaline (20 mg/kg, i.p.).

One of the issues associated with antipsychotic drugs is the potential to develop extrapyramidal symptoms (EPS), which can be assessed in mice by measuring the induction of catalepsy using the bar test. Oral administration of SEP-856 (100 mg/kg) produced no effects in the bar test, whereas haloperidol (1 mg/kg, i.p.) significantly increased the amount of time mice spent holding the bar at 30- and 90-minute postdosing (two-way ANOVA: treatment effect F(2, 54) = 107.7, P < 0.0001; time effect F(1, 54) = 9.4, P < 0.005; Dunnet’s post hoc test, P < 0.05). Importantly, these data indicate that SEP-856 was not associated with cataleptic effects at doses at least 30-fold higher than efficacious dose levels in mice (Fig. 3E).

The plasma and brain exposures to SEP-856 in the mouse PCP-induced hyperactivity and PPI tests as well as the rat subchronic PCP-induced social interaction test are shown in Supplemental Table 6. Taken together, our results indicate that SEP-856 decreases REM sleep in rats. (A) Acute, oral administration of SEP-856 led to a dose-dependent reduction in cumulative REM sleep (A), increase in latency to REM (B), and a decrease in REM/non-REM ratio (C) in Sprague-Dawley rats over the 6-hour recording period (one-way repeated-measures ANOVA + two-tailed t test, *P < 0.05 vs. Veh). Dosing occurred in the middle of the inactive phase, at the beginning of Zeitgeber time 7. The positive control caffeine (10 mg/kg, p.o. CAF) produced similar effects on REM time and latency without altering the REM/non-REM ratio. Additional parameters are presented in Supplemental Fig. 4. N = 7. Data are shown as mean ± S.E.M.
was conducted in two anesthetized baboons using the radiotracer [18F]-fallypride. The percent occupancy was evaluated using a blockade protocol comparing [18F]-fallypride regional binding potential at baseline and following SEP-856 administration (∼7.25 mg/kg, i.v. 30 minutes prior to [18F]-fallypride injection). Venous blood samples were taken before and at various time points after SEP-856 administration. SEP-856 showed D2 receptor occupancy levels of 9.1% ± 3.3%, 6.2% ± 6.1%, and 9.6% ± 8.8% in the caudate, putamen, and globus pallidus, respectively (Fig. 5; Supplemental Table 8). Similar to the observations in rats, SEP-856 did not produce significant occupancy at D2 receptors despite achieving high plasma concentrations (i.e., 2850 ± 250 ng/ml at 60 minutes and 1765 ± 125 ng/ml at 180 minutes after SEP-856 administration). Importantly, this finding demonstrates that the antipsychotic-like behavioral profile of SEP-856 is independent of direct D2 receptor modulation.

Next, we used in vitro autoradiography to evaluate the effects of SEP-856 on [3H]-8-OH-DPAT (a 5-HT1A agonist radioligand) binding to 5-HT1A receptors in the rat brain. Slide-mounted rat brain sections were incubated with 2 nM [3H]-8-OH-DPAT in the presence and absence of SEP-856 (0.1, 1, and 10 µM). Nonspecific binding was defined by 10 µM 5-HT. SEP-856 produced a concentration-dependent displacement of [3H]-8-OH-DPAT binding in all regions evaluated (Supplemental Fig. 5). Given the similar degree of [3H]-8-OH-DPAT binding in all brain areas, IC50 values for SEP-856 displacement of [3H]-8-OH-DPAT binding were only determined for the septum and motor/somatosensory cortex (referred to as cortex). SEP-856 displaced [3H]-8-OH-DPAT in a concentration-dependent manner, with a mean IC50 of 619 and 791 nM in the cortex and septum, respectively (Fig. 6). Similar to the observations in rats, SEP-856 did not produce significant occupancy at 5-HT1A receptor sites in vitro.

SEP-856 Inhibits Neuronal Firing in the DRN and VTA In Vitro. To investigate the effect of SEP-856 on neuronal activity and obtain further insights into its mechanism of action, we performed whole-cell patch-clamp recordings in isolated slice preparations of the DRN and the VTA of C57BL/6J mice. The DRN and VTA express a high abundance of 5-HT1A and TAAR1 receptors, respectively (Lindemann et al., 2008; Celada et al., 2013; Christian and Berry, 2018). After the determination of repeatable responses, administration of SEP-856 was repeated in the presence of the selective TAAR1 antagonist EPPTB and/or the selective 5-HT1A receptor antagonist WAY-100635.

Whole-cell current-clamp recordings were made from 29 neurons within the DRN with a mean resting membrane potential of −46.1 ± 1.0 mV and a mean input resistance of 849 ± 61 MΩ. Based on changes in membrane potential and firing rates, 16 of the DRN neurons were characterized as being sensitive to the 5-HT1A agonist 8-OH-DPAT (DPAT), and 13 were classified as DPAT-insensitive (Supplemental Fig. 6). Based on their initial threshold activity, 44% (7 of 16) of DPAT-sensitive neurons were characterized as spontaneously active (discharging action potentials) and 56% (9 of 16) were quiescent. SEP-856 (10 µM) induced significant membrane hyperpolarization in eight of nine quiescent neurons (45.5 ± 1.9 to −49.0 ± 2.2 mV, post–SEP-856 washout to 46.1 ± 1.9 mV; paired two-tailed t test, t4 = 4.3, P = 0.004; Fig. 7A). In contrast, one single neuron was depolarized by 2.1 mV. SEP-856 also significantly reduced the activity of five of seven spontaneously active DRN neurons (0.31 ± 0.10 Hz to 0.11 ± 0.04, post–SEP-856 washout to 0.20 ± 0.06 Hz; 69% ± 9.7% reduction; paired two-tailed t test, t4 = 3.2, P = 0.03; Fig. 7A), whereas the remaining two neurons were largely unaffected. Collectively, administration of 10 µM SEP-856 induced an inhibitory response, determined by either a membrane hyperpolarization or a reduction in spontaneous firing rate, in 81% (13 of 16) of DPAT-sensitive neurons. In contrast, SEP-856 only induced an inhibitory response in 15% (2 of 13) of DPAT-insensitive neurons (Supplemental Fig. 6).

Next, the effects of 10 µM SEP-856 were examined in the presence of the 5-HT1A antagonist WAY-100635 (1 µM) in five DPAT-sensitive DRN neurons, two of which were spontaneously active and three of which were quiescent. In three of the five neurons, a membrane hyperpolarization of 1.9 ± 0.4 mV induced by SEP-856 was markedly reduced to 0.4 ± 0.1 mV when SEP-856 was reapplied in the presence of WAY-100635 (79% reduction; Fig. 7B; Supplemental Fig. 6). Similarly, the inhibitory effect of SEP-856 was almost completely blocked in a further neuron in the presence of WAY-100635, with the spontaneous firing rate being reduced by 47% (0.21–0.11 Hz) during control SEP-856 administration compared with just a 2% reduction (0.83–0.82 Hz) when SEP-856 was applied in the presence of WAY-100635 (Fig. 7B). In the remaining neuron, a 2.4 mV hyperpolarization induced by SEP-856 was slightly increased to 2.6 mV in the presence of WAY-100635. Thus, the inhibitory response induced by SEP-856 was reduced in the presence of the 5-HT1A antagonist WAY-100635, in the majority (4 of 5, 80%) of DRN neurons analyzed.

In addition, the effects of SEP-856 were examined in the presence of EPPTB in six DPAT-sensitive DRN neurons, three of which were spontaneously firing action potentials and three of which were quiescent. Overall, the inhibitory response induced by SEP-856 was unaffected in the presence of the

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**Fig. 5.** SEP-856 does not exhibit significant occupancy at D2 receptors in nonhuman primates. Representative magnetic resonance (for anatomic reference) and mean summed positron emission tomography images, before and after administration of SEP-856, are shown from top to bottom for one animal. Axial, sagittal, and coronal slices are shown from left to right. Regions of interest, including the caudate, putamen, and globus pallidus, were manually outlined. Average [18F]fallypride positron emission tomography images over 180 minutes of acquisition are presented at baseline and following bolus i.v. administration of SEP-856 (7.25 mg/kg). The occupancy was estimated using the BPND-derived Simplified Reference Tissue Model. SUVr, relative standardized uptake value.
TAAR1 antagonist EPPTB, in the majority (5 of 6, 83%) of DRN neurons tested (Fig. 7C).

Following the assessment of SEP-856 effects on DRN neuronal firing, whole-cell patch-clamp recordings were also made from 23 neurons within the VTA (mean resting membrane potential of $-40.7 \pm 0.7$ mV and a mean input resistance of $935 \pm 104 \text{MO}$) (Supplemental Fig. 7). All of these neurons were spontaneously active once whole-cell configuration had been established with a mean firing rate of $1.97 \pm 0.60$ Hz, although activity did not persist in all cases. SEP-856 induced an inhibitory response in approximately half of the recorded VTA neurons (Fig. 7D; Supplemental Fig. 7). This response was characterized by a significant hyperpolarization of $2.8 \pm 0.5$ mV in 42% (8 of 19) of the neurons ($-42.6 \pm 1.3$ to $-45.3 \pm 1.4$ mV; paired two-tailed t test, $t_p = 5.8, P = 0.0007$) and a significant reduction in spontaneous firing rate in 55% (11 of 20) of the neurons (from $0.6 \pm 0.18$ to $0.18 \pm 0.07$ Hz; 71.4% ± 7% reduction; paired two-tailed t test, $t_{10} = 3.3, P < 0.008$; Fig. 7D).

Interestingly, recordings from two neurons showed that the inhibitory response of SEP-856 (1 $\mu$M) was reduced in the presence of 1 $\mu$M EPPTB (Fig. 7F), but persisted in the presence of the 5-HT$_{1A}$ antagonist WAY-100635 (Fig. 7E). However, observations from additional neurons are necessary to further validate the ability of EPPTB to attenuate the inhibitory effect of SEP-856 in the VTA.

Overall, SEP-856 induced significant inhibitory responses in DPAT-sensitive neurons of the DRN and a subset of VTA neurons. In contrast to the inhibitory effects of SEP-856 in the DRN, which were primarily mediated via activation of 5-HT$_{1A}$ receptors, the response in the VTA appeared to be at least partially mediated via the activation of TAAR1.

SEP-856 Inhibits DRN Neuronal Firing In Vivo. The observation that SEP-856’s inhibitory effects in the DRN were mediated by 5-HT$_{1A}$ led us to additionally investigate DRN neuronal firing in vivo by recording extracellular single-unit activities in anesthetized Sprague-Dawley rats. In accordance with previous work (Martin et al., 1999), application of 8-OH-DPAT inhibited DRN firing, which was subsequently reversed by 0.08 mg/kg WAY-100635 (Supplemental Fig. 8). SEP-856 (2 mg/kg, i.v.) significantly decreased DRN neuron discharges to 87% of the baseline rate (from $9.83 \pm 1.4$ to $1.4 \pm 0.33$ spikes/10 seconds; two-tailed t test, $t_2 = 5.9, P < 0.03$) during the initial 10 minutes postdosing (Fig. 8, A and B). Thirty minutes after SEP-856 administration, the inhibitory effect was no longer detectable and firing rates were restored to baseline levels. SEP-856 plasma exposures determined 30 minutes postdosing were $422 \pm 22.5 \text{ng/ml}$. When SEP-856 was tested at a higher dose (5 mg/kg, i.v.), firing activity was completely suppressed and the inhibition was fully reversed by intravenous administration of $0.08 \text{mg/kg}$ WAY-100635 (Fig. 8, C and D). Similarly, the inhibitory effect of 2 mg/kg SEP-856 was also reversed by WAY-100635 (Supplemental Fig. 8). These results support the earlier in vitro finding in mice, and further suggest that part of SEP-856’s mechanism of action is characterized by suppression of serotonergic neuronal firing via activation of 5-HT$_{1A}$ autoreceptors.

SEP-856 Does Not Alter Dopamine and Serotonin Release in the Striatum or Prefrontal Cortex. To determine whether the inhibitory action of SEP-856 in DRN neurons translates into changes in synaptic serotonin levels, we measured 5-HT release in vivo using microdialysis in freely-moving rats. Although SEP-856 demonstrated no occupancy at D$_2$ receptors in vivo, its antipsychotic-like behavioral profile, TAAR1 activity, and ability to inhibit VTA neurons suggest potential modulation of dopaminergic circuits independent of direct dopamine receptor regulation. We therefore also assessed dopamine release. Changes in monoamine levels were monitored over a 240-minute period following oral administration of vehicle, 3, 10, or 30 mg/kg SEP-856. Interestingly, no significant changes in extracellular levels of dopamine or 5-HT were observed in striatum or prefrontal cortex following SEP-856 administration (Supplemental Fig. 9).

Antipsychotic-Like Effects of SEP-856 Are Partially Mediated by 5-HT$_{1A}$ Receptors. Although the microdialysis findings revealed no changes in SEP-856–mediated 5-HT release, the in vivo pharmacology results as well as the slice and in vivo electrophysiology data suggest that agonism at 5-HT$_{1A}$ receptors is integral to SEP-856’s mechanism of action in both mice and rats. Consequently, we evaluated whether the 5-HT$_{1A}$ receptor antagonist WAY-100635 would attenuate the inhibitory behavioral effects of SEP-856 in the mouse PCP-induced hyperactivity test. C57BL/6J mice were injected with
WAY-100635 (1 mg/kg, i.p.) or saline (i.p.) 10 minutes prior to SEP-856 dosing (3 mg/kg, oral), followed by PCP administration (5 mg/kg, i.p.) 30 minutes later. Consistent with our previous findings, single oral administration of SEP-856 significantly inhibited PCP-induced hyperactivity responses (Fig. 8E). Pretreatment with WAY-100635 partially attenuated the inhibitory effects of SEP-856 on the total distance traveled (one-way ANOVA $F(5, 51) = 22.11$, $P < 0.0001$; Tukey’s post hoc test, $P < 0.05$). Taken together, the results indicate that the antipsychotic-like effects of SEP-856 in the PCP-induced hyperactivity test may be partially mediated through 5-HT$_{1A}$ receptors.

Fig. 7. SEP-856 inhibits firing of DRN and VTA neurons in vitro. Representative whole-cell patch-clamp recordings from DRN and VTA brain slices of C57BL/6J mice are shown on the left, and quantification histograms on the right. Compound-induced effects were determined based on significant changes in membrane potential (millivolts) and/or firing rate (Hertz) and expressed relative to baseline ($\Delta$ membrane potential and % frequency change). DRN neurons were classified as sensitive or insensitive to the 5-HT$_{1A}$ agonist 8-OH-DPAT. (A) SEP-856 induced inhibitory responses in the majority of spontaneously active, 8-OH-DPAT-sensitive DRN neurons. This inhibitory effect was absent in four of five neurons in the presence of the 5-HT$_{1A}$ antagonist WAY-100635 (B) but persisted in five of six neurons in the presence of the TAAR1 antagonist EPPTB (C). (D) Based on significant changes in membrane potential and/or firing rate, approximately half of the spontaneously-active neurons in the VTA were inhibited by SEP-856 treatment when compared with baseline. This effect persisted in presence of WAY-100635 (E, $n = 2$ neurons) but was reduced in the presence of EPPTB (F, $n = 2$ neurons). Histograms show neuronal responses following administration of SEP-856 alone (control, A and D) and in the presence of WAY-100635 (B and E) or EPPTB (C and F). Solid horizontal bars indicate the time frame of compound administration to the slice. Two-tailed $t$ test, *$P < 0.05$. Abbreviations: WAY-100635 (WAY or WAY-635). Data are shown as mean ± S.E.M.
**Discussion**

Numerous advances have been made in understanding the potential role of receptors other than D2 in contributing to drug efficacy and specific side effects in schizophrenia. Recent antipsychotic drug development has focused on non-D2 targets, including D1, D4, D3, NMDA, 5-HT2A, 5-HT2C, M1, M4, H3, NK3, and σ receptors (Miyamoto et al., 2005; Karam et al., 2010; Girgis et al., 2019). However, to date, no compound lacking D2 receptor blockade has proven effective for any symptom dimension of schizophrenia. Although several non-D2 mechanisms, including mGlu2/3 receptor agonism and GlyT1 inhibition, have demonstrated efficacy in nonclinical and clinical proof-of-concept studies, positive results in Phase III clinical trials are still lacking (Marsman et al., 2013; Kinon et al., 2015; Girgis et al., 2019). However, to date, no compound lacking D2 receptor blockade has proven effective for any symptom dimension of schizophrenia. Although several non-D2 mechanisms, including mGlu2/3 receptor agonism and GlyT1 inhibition, have demonstrated efficacy in nonclinical and clinical proof-of-concept studies, positive results in Phase III clinical trials are still lacking (Marsman et al., 2013; Kinon et al., 2015; Girgis et al., 2019). In this study, we used an in vivo mouse phenotypic screening platform in combination with comprehensive in vitro and in vivo profiling to identify compounds that exhibited behavioral similarity to known antipsychotics but do not act through D2 or 5-HT2A mechanisms. This led to the discovery of SEP-856, a compound that showed potent antipsychotic-like properties without inducing catalepsy. In addition, SEP-856 demonstrated potential antidepressant-like effects, suppressed REM sleep, and modulated firing in a subset of VTA and DRN neurons.

To decipher the molecular mechanism of action (MOA) of SEP-856, its effects were initially studied in panel screens of large numbers of receptors, ion channels, and enzymes. Subsequent studies identified activity at TAAR1, 5-HT1A, 5-HT1D, α2A, and D2 receptors. Weak partial agonism of D2 receptors (EC50 = 8–10 μM, Emax 24%–27%), and some very low-potency antagonism (34% inhibition at 100 μM), was seen in vitro assays. It should be noted that this antagonism was assay dependent as, for instance, no antagonist response was seen in the β-arrestin recruitment assay. Despite this in vitro activity, additional experiments indicated that the MOA of SEP-856 does not include in vivo blockade at D2 given the lack of receptor occupancy in rat and monkey seen at doses/exposures that are efficacious in rodent behavioral assays. Furthermore, the demonstrated central occupancy of 5-HT1A receptors, as well as the partial reversal of PCP-induced hyperactivity in the presence of WAY-100635, indicates that 5-HT1A agonism contributes to the MOA of SEP-856. This was further supported by SEP-856’s ability to induce significant inhibitory responses via 5-HT1A receptors in putative serotonergic neurons in the DRN in vitro and in vivo. Notably, the inhibitory response induced in a subset of VTA neurons was mediated, at least in part, via activation of TAAR1, suggesting that SEP-856 modulates firing of putative serotonergic and dopaminergic neurons through distinct mechanisms.

TAAR1 is a GPCR activated by trace amines and expressed in multiple regions of the mammalian brain, including the limbic system, DRN and VTA (Borowsky et al., 2001; Burchett and Hicks, 2006; Lindemann et al., 2008; Rutigliano et al., 2018). Recent studies have extensively characterized TAAR1 functions, elucidating its important role in modulating dopaminergic circuitry and its potential implications in neuropsychiatric disorders (Borowsky et al., 2001; Leo et al., 2014;
nergic signaling presumably occur via functional physical transmission makes it an interesting target for a number of psychiatric disorders (Lindemann et al., 2008; Revel et al., 2011; Leo et al., 2014). Along these lines, TAAR1 agonists have been reported to suppress VTA neuronal firing (Revel et al., 2011) and inhibit dopamine specifically in the nucleus accumbens but not in the dorsolateral striatum of TAAR1 KO mice (Lindemann et al., 2008). Follow-up work by Leo et al. (2014), using microdialysis and fast-scan cyclic voltammetry, revealed increased levels of dopamine specifically in the nucleus accumbens but not in the dorsal striatum of TAAR1 KO mice (Lindemann et al., 2008).

In accordance, TAAR1 agonists have been reported to suppress VTA neuronal firing (Revell et al., 2011) and inhibit electrically-evoked dopamine release (Leo et al., 2014). SEP-856 exerted inhibitory effects in VTA neurons, which were likely mediated via activation of TAAR1. Interestingly, the inhibitory response was only observed in half of the recorded cells, pointing to a selective suppression of a subset of VTA neurons by SEP-856. The lack of D2 occupancy, in addition to the inhibitory effects on VTA neuronal firing, potentially suggests modulation of presynaptic dopamine dysfunction by SEP-856. Abnormalities in dopamine synthesis capacity, baseline synaptic dopamine levels, and dopamine release have been reported in schizophrenia patients, and are not targeted by current antipsychotic treatments (Bowles et al., 2012; Jauhar et al., 2017; Kim et al., 2017; McCutcheon et al., 2018). Although SEP-856 demonstrated clear inhibitory effects on DRN and VTA neurons, it did not alter dopamine or 5-HT release in the striatum or prefrontal cortex. This could be due to a number of reasons, including the difficulty in detecting potential decreases in neurotransmitter release under baseline conditions using conventional microdialysis. Differential effects of SEP-856 on dopamine and/or serotonin release might primarily be detectable under stimulated conditions (e.g., following electrical, pharmacological, or behavioral challenges) or in a disease context (e.g., hyperdopaminergic state). In contrast, changes in dopaminergic and serotonergic cell firing do not necessarily translate into changes in dopamine/5-HT release (Berke, 2018). For example, dopamine release can be locally controlled by the presynaptic terminals themselves and thus show spatiotemporal patterns independent of cell body spiking (Floresco et al., 1998; Jones et al., 2010; Berke, 2018). In addition, SEP-856 might affect tonic versus phasic dopaminergic firing differentially, which could ultimately result in marked behavioral effects without necessarily altering overall dopamine levels. Additional experiments, applying both microdialysis and fast-scan cyclic voltammetry, will help to further elucidate the effect of SEP-856 on neurotransmitter release and firing kinetics under baseline and stimulated conditions.

In addition to TAAR1-mediated activity, 5-HT1A agonism was identified as an integral part of the MOA of SEP-856. The 5-HT1A receptor is highly expressed in the DRN, cortex, and limbic forebrain areas (e.g., hippocampus and amygdala), with lower densities detected in the basal ganglia, thalamus, substantia nigra, and VTA (Kia et al., 1996; Itou et al., 1999; De Almeida and Mengod, 2008). In the DRN, 5-HT1A receptors are primarily somatodendritic autoreceptors that function to inhibit neuronal firing. In contrast, they are present as postsynaptic receptors in the hippocampus and amygdala (Celada et al., 2013). Thus, it will be interesting to test whether SEP-856 also acts in an inhibitory fashion in forebrain regions such as the hippocampus or prefrontal cortex.

The serotonergic circuitry has repeatedly been implicated in the pathophysiology of schizophrenia, in part due to the antipsychotic properties of 5-HT2A antagonists (although primarily in combination with D2 blockers). In addition, 5-HT2C antagonists and compounds that target both receptors 5-HT2A/5-HT2C (e.g., ritanserin, vabicaserin, mianserin, SR46349B, etc.) have demonstrated some efficacy in schizophrenia (Girgis et al., 2019). Although evidence exists for the therapeutic efficacy of 5-HT1A agonists in depression and anxiety, less is known about the potential contribution of these receptors to schizophrenia. Postmortem (Burnet et al., 1996, 1997; Simpson et al., 1996; Sumiyoshi et al., 1996) and neuroimaging studies (Kasper et al., 2002; Tauscher et al., 2002) have revealed alterations in 5-HT1A receptor density in the cortex and amygdala of schizophrenic patients (Yasuno et al., 2004). Evidence in rodent models indicates that the activation of 5-HT1A receptors prevents EPS induced by D2 receptor blockade, modulates dopaminergic neurotransmission in the frontal cortex, positively influences mood, and attenuates NMDA receptor antagonist-induced cognitive and social interaction deficits (Newman-Tancredi, 2010; Celada et al., 2013). In addition, a number of compounds that combine partial agonism at 5-HT1A receptors with antagonism (or partial agonism) at D2 receptors (e.g., aripiprazole, perospirone, lurasidone, cariprazine, PF-217830, F-97013-GD, F-15063, and bifeprunox) appear to provide therapeutic benefits against a broader range of schizophrenia symptoms (Newman-Tancredi, 2010; Celada et al., 2013).

Interestingly, earlier work demonstrated that modulation of TAAR1 activity via the selective agonist RS5166017 increases the potency of 5-HT1A partial agonists and alters the desensitization rate at the 5-HT1A autoreceptors in the DRN.
This can occur by direct interaction of TAAR1 and 5-HT1A receptors (Tribl et al., 2013; Wichniak et al., 2017; Goonawardena et al., 2019). Thus, the robust REM suppression observed with SEP-856 could result from synergistic action on TAAR1 and 5-HT1A receptors. However, agonism at TAAR1 and 5-HT1A receptors might only partially contribute to SEP-856’s MOA, with other (possibly not yet identified) targets likely playing key roles as well.

Although this work made use of multiple pharmacological rodent models and assays, it is important to mention that no animal model is, or ever will be, truly reflective of the underlying disease etiology of schizophrenia. Nevertheless, certain models serve as important investigational tools and are useful in the development of novel treatments, especially when the goals for a specific model and/or approach are clearly defined (Nestler and Hyman, 2010). Our goal was to identify a novel MOA for the treatment of schizophrenia by focusing on a desired clinical outcome—the combination of antipsychotic efficacy and lack of D2-mediated side effects (e.g., EPS and endocrine effects). Ultimately, proof-of-concept studies in humans are required to determine whether preclinical findings will translate into therapeutic efficacy. SEP-856 is currently being evaluated for the treatment of schizophrenia in randomized, controlled clinical trials.

In summary, the approach used in this work represents an alternative to target-driven drug discovery as it relied on in vivo phenotypic and in vitro (anti-target) screening, followed by subsequent verification in putative animal models of schizophrenia. Accordingly, the MOA of SEP-856 has not been fully elucidated. However, the selective agonism of TAAR1 and 5-HT1A, in addition to the lack of D2/5-HT2A-mediated efficacy, has the potential to translate into a significantly improved safety profile compared with available therapies, while still maintaining antipsychotic efficacy across a broad array of symptoms. Based on its unique MOA and preclinical profile in animals, SEP-363856 represents a promising candidate for the treatment of schizophrenia and potentially other neuropsychiatric disorders.

Acknowledgments

This manuscript is dedicated to the memory of a beloved colleague, Dr. Una C. Campbell.

Authorship Contributions


References


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