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ORIGINAL INVESTIGATION

Sigma-1 receptor ligand PD144418 and sigma-2 receptor ligand YUN-252 attenuate the stimulant effects of methamphetamine in mice

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Abstract

Rationale Previous research indicates that the selective sigma-1 receptor ligand PD144418 and the selective sigma-2 ligands YUN-252 can inhibit cocaine-induced hyperactivity. The effects of these ligands on other stimulants, such as methamphetamine, have not been reported.

Objectives The present study examined the effects of PD144418 and YUN-252 pretreatment on methamphetamine-induced hyperactivity after acute treatment.

Methods Mice ($n = 8$–14/group) were injected with PD144418 (3.16, 10, or 31.6 μmol/kg), YUN-252 (0.316, 3.16, 31.6 μmol/kg), or saline. After 15 min, mice injected with 2.69 μmol/kg methamphetamine or saline vehicle, where distance traveled during a 60-min period was recorded. Additionally, the effect of PD144418 on the initiation and expression of methamphetamine sensitization was determined by treating mice ($n = 8$–14/group) with PD144418, methamphetamine or saline repeatedly over a 5-day period, and testing said mice with a challenge dose after a 7-day withdrawal period.

Results Results indicate that both PD144418 and YUN-252, in a dose-dependent manner, attenuated hyperactivity induced by an acute methamphetamine injection. Specifically, 10 μmol/kg or 31.6 μmol/kg of PD144418 and 31 μmol/kg of YUN-252 suppressed methamphetamine-induced hyperactivity. In regard to methamphetamine sensitization, while 10 μmol/kg PD144418 prevented the initiation of methamphetamine sensitization, it did not have an effect on the expression.

Conclusions Overall, the current results suggest an intriguing potential for this novel sigma receptor ligand as a treatment for the addictive properties of methamphetamine. Future analysis of this novel sigma receptor ligand in assays directly measuring reinforcement properties will be critical.

Keywords Sigma receptor · Methamphetamine · Locomotor activity

The Use of illicit drugs, such as methamphetamine, is a health concern across the USA. However, there are currently no pharmacological treatment options to specifically treat methamphetamine addiction. Methamphetamine, a psychostimulant, works by elevating extracellular monoamine neurotransmitters, including dopamine, via multiple pathways (Sulzer et al. 2005). In addition to its effects on dopamine, methamphetamine can also elicit effects via sigma (σ) receptors (Nguyen et al. 2005; Yasui and Su 2016).

The sigma receptor, a non-opioid receptor, exists in two distinct forms, sigma-1 (σ_1) and sigma-2 (σ_2) (Hayashi and Su 2004). Both receptors are expressed widely throughout the brain, including areas involved in motor functions, sensory perception, learning, and motivation (Alonso et al. 2000; Hayashi and Su 2004; Martin-Fardon et al. 2007). The σ_1 receptor has been implicated as a potential target for psychiatric disorders including schizophrenia (Ohi et al. 2011), addiction (Blasio et al. 2015; Maurice et al. 2002, 2003; Robson et al. 2012; Romieu et al. 2002; Sabino et al. 2009b, 2011;

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Sambo et al. 2017), anxiety (Hashimoto 2015; Ji et al. 2016), and depression (Fukunaga and Moriguchi 2017; Hashimoto 2015; Liu et al. 2017; Nguyen et al. 2014; Sabino et al. 2009a). The σ_2 receptor has been implicated similarly in addiction (Katz et al. 2016; Klawonn et al. 2017; Scott et al. 2018), and possesses antidepressant-like properties (Sanchez and Papp 2000). In regard to σ receptor implications in addiction, psychostimulants, such as methamphetamine, have been predominately studied (Hayashi et al. 2010; Matsumoto et al. 2008; Rodvelt and Miller 2010; Sambo et al. 2017; Stefanski et al. 2004; Ujike et al. 1992), as methamphetamine binds at physiologically relevant concentrations to σ_1 receptors (2–4 μM) (Nguyen et al. 2005; Yasui and Su 2016) and σ_2 receptors (16–47 μM) (Nguyen et al. 2005; Yasui and Su 2016).

With this knowledge, subtype-selective ligands have been synthesized to further characterize the role of each in neurochemical and behavioral processes. Two σ_1 ligands that have been studied extensively in regard to behavior are BD1047 and BD1063 (Lever et al. 2014; Nguyen et al. 2005; Sambo et al. 2017). While BD1047 and BD1063 both have a 100-fold or better affinity for sigma binding sites, BD1047 also shows a significant affinity for β-adrenoceptors (Matsumoto et al. 1995). Additionally, when measuring the affinity for σ_1 binding sites compared to σ_2 binding sites, BD1047 and BD1063 show only a 51-fold and 49-fold greater affinity for σ_2 sites compared to σ_2 sites, respectively (Matsumoto et al. 1995). However, PD144418 [1,2,3,6-tetrahydro-5-[3-(4-methylphenyl)-5-isoxazolyl]-1-propylpyridine] has been characterized as a more potent and selective σ_1 ligand, as it exhibits a high affinity for σ_1 receptors (Ki = 0.08 nM) and has a 17,000-fold selectivity for the σ_1 subtype over the σ_2 subtype (Ki = 1377 nM) (Akunne et al. 1997; Lever et al. 2014). Moreover, PD144418 has week interactions with monoamine transporters, including the dopamine transporter (DAT) (Ki = 9 μM), norepinephrine transporter (Calcagnetti and Schechter 1993) (> 100 μM), and the serotonin transporter (SERT) (> 100 μM) (Lever et al. 2014). Based on these findings, the effects PD144418 on rodent behavior have been examined. In rodent behavioral studies, PD144418 has been found to produce a dose-dependent attenuation of locomotor activity of stimulants, such as cocaine (Lever et al. 2014). Mice administered 3.16 or 10 μmol/kg PD144418 followed by cocaine were less active (~45%) than mice administered saline followed by cocaine (Lever et al. 2014). Additionally, at 31.6 μmol/kg, PD144418 inhibited cocaine-induced hyperactivity by ~85% (Lever et al. 2014)

In regard to σ_2 ligands, investigation appears to be critically dependent on the ligand of study. For instance, (±)-SM 21, which has been described as a σ_2 preferring antagonist and can attenuate cocaine-induced locomotor activity, only has a 10-fold preferential affinity for the σ_2 receptor subtype over the σ_1 subtype and has a comparable affinity for dopamine transporters (Matsumoto et al. 2007). SN79, a σ_2 ligand, also attenuates cocaine's stimulatory effects and has a high affinity for the σ_2 receptor (Ki = 7 nM) but only has a fourfold selectivity against the σ_1 receptor (Kaushal et al. 2011). YUN-252 (5-bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl)]-2,3-dimethoxy-benzamide) has been found to have a 1000-fold selectivity for the σ_2 receptor subtype over the σ_1 subtype (Ki values = 8.2 nM and 12,900 nM, respectively) (Mach et al. 2004). In addition, YUN-252 has low binding affinities (Ki values > 10,000 nM) to DAT and NET and moderate binding affinity to SERT (Ki = 154 nM) (Lever et al. 2014). In examining the effects of YUN-252 on cocaine-induced hyperactivity, a high dose (31.6 μmol/kg), but not a low dose (3.16 μmol/kg), dose attenuated (~66%) cocaine-induced hyperactivity (Lever et al. 2014).

Whereas research indicates that the selective σ_1 ligand PD144418 and the selective σ_2 ligands YUN-252 can dose attenuate cocaine-induced hyperactivity, the effect of such ligands on other stimulants, such as methamphetamine, has not been reported. Therefore, the goal of the present study is to examine the effects of PD144418 and YUN-252 pretreatment on hyperactivity induced by acute methamphetamine treatment (experiment 1 and experiment 2). Additionally, the effect of PD144418 on methamphetamine-induced hyperactivity after acute and repeated drug administration was determined (experiment 3). This was achieved by examining the effects of PD144418 on the initiation phase of locomotor sensitization development. Furthermore, the effects of PD144418 on the expression phase that occurs after the development of locomotor sensitization were determined.

Materials and methods

Subjects

Male CD-1 mice (Charles River Laboratories International, Inc., Wilmington, MA) typically 20–22 g at arrival were group housed 4 or 5 mice per cage with standard rodent chow and water available ad libitum. The colony was maintained under a 12-h light/dark cycle. Experiments were conducted in the light phase of the cycle after the animals had acclimated to the colony room for a week. Studies were performed with procedures approved by the Institutional Animal Care and Use Committee of the University of Missouri Columbia.

Drugs and chemicals

Throughout the manuscript, all drug weights represent the free base weight. PD144418 oxalate was obtained from Tocris Bioscience (Minneapolis, MN) and the stock solution was prepared as described in the literature by Lever et al. (2014). (+)-Methamphetamine hydrochloride was purchased from

Sigma-Aldrich (Saint Louis, MO). YUN-252 was prepared as the hemioxlate salt according to the method described in the literature (Mach et al. 2004). Throughout the manuscript, the doses of PD144418 and YUN-252 are presented in μmol units to allow for comparison to other sigma ligands. All drugs were prepared in saline (0.9% *w*/*v*) vehicle. PD144418 [3.16 μmol/kg = 1.18 mg/kg, 10 μmol/kg = 3.72 mg/kg, 31.6 μmol/kg = 11.77 mg/kg], YUN-252 [0.316 μmol/kg = 0.16 mg/kg, 3.16 μmol/kg = 1.60 mg/kg, 31.6 μmol/kg = 16.03 mg/kg], and methamphetamine [2.69 μmol/kg = 0.5 mg/kg] were administered intraperitoneally (i.p.).

Apparatus

Experiments were performed in automated activity monitors (Model ENV-515; Med Associates Inc., Georgia, VT) consisting of a transparent box surrounded by banks of infrared sensors that were connected to a computer. Data were collected using Med Associates' Open Field Activity Software (SOF-811) that records the number of sensor breaks and computes these data to measures of distance traveled (in cm).

Experiments 1 and 2: acute effects of PD144418 and YUN-252 on methamphetamine locomotor activity

The effect of PD144418 and YUN-252 on methamphetamine-induced hyperactivity was determined by procedures similar to those used previously (Lever et al. 2014; Rodvelt et al. 2011; Sage et al. 2013). Mice ($n = 156$) were divided into 16 groups [(saline + saline [PD144418] ($n = 14$); saline + methamphetamine (2.69 μmol/kg) [PD144418] ($n = 12$); PD144418 (3.16 μmol/kg) + saline ($n = 8$); PD144418 (3.16 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 7$); PD144418 (10 μmol/kg) + saline; ($n = 9$) PD144418 (10 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 12$); PD144418 (31.6 μmol/kg) + saline ($n = 7$); PD144418 (31.6 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 8$); saline + saline [YUN-252] ($n = 14$); saline + methamphetamine (2.69 μmol/kg) [YUN-252] ($n = 10$); YUN-252 (0.3 μmol/kg) + saline ($n = 8$); YUN-252 (0.3 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 11$); YUN-252 (3 μmol/kg) + saline ($n = 8$); YUN-252 (3 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 12$); YUN-252 (31 μmol/kg) + saline ($n = 8$); YUN-252 (31 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 8$)] and were acclimated to the animal colony for at least 1 week after arrival. Prior to testing, mice were acclimated to the monitors for 30–60 min on two consecutive days. On the third day, locomotor activity was measured. Mice were placed into the monitors for 45 min, injected with PD144418 (3.16, 10, or 31.6 μmol/kg), YUN-252 (0.316, 3.16, 31.6 μmol/kg), or saline. Mice were returned to the monitor for 15 min, injected with 2.69 μmol/kg methamphetamine or saline vehicle, and then returned to the monitor for 60 min. Distance traveled (in cm) during the 60-min period was recorded. While a single dose is a limiting factor compared to a dose -response analysis, the methamphetamine dose was selected based on previous work demonstrating a consistent significant increase relative to saline-treated animals in locomotor activity after acute injection of mice (Miller et al. 2013). Moreover, Nguyen et al. (2005) showed, using a dose -response (e.g., 0.1, 0.5, 1, 3, 5, 10 mg/kg), that acute administration of methamphetamine produced a dose-dependent effect on locomotor activity, with a peak at 1 mg/kg, i.p. Therefore, we can conclude that any effects of PD144418 and YUN-252 that may be observed in regard to acute methamphetamine administration are due to a decrease in the stimulant actions of methamphetamine. PD14418 and YUN-252 doses were selected based upon previous work by Lever et al. (2014) as doses that attenuate cocaine -induced locomotor activity.

Analysis using a two-way ANOVA, with the dose of PD144418 and saline or methamphetamine (2.69 μmol/kg), was used to examine the total distance traveled. Additionally, a three-way repeated measures ANOVA (RM-ANOVA), with time as the within-subject factor and methamphetamine and PD144418 or YUN-252 as the between -subject factors, was used to determine the effect of PD144418 or YUN-252 on basal locomotor activity and methamphetamine-induced locomotor hyperactivity over 12 5-min increments. When appropriate ($p < 0.05$), a simple main effect analysis and post hoc comparisons, using a Bonferroni correction, were made.

Experiment 3: effect of PD14418 on methamphetamine sensitization

The effect of PD144418 on the initiation and expression of locomotor sensitization to methamphetamine was determined using the procedures described below.

Initiation To assess the effects of PD14418 on the initiation of methamphetamine sensitization (Table 1), mice ($n = 61$) were divided into six groups, of which three groups received saline + PD144418 (0 μmol/kg, 3.16 μmol/kg, or 10 μmol/kg) during the initiation phase, while the other three groups received methamphetamine (2.69 μmol/kg) + PD144418 (0 μmol/kg, 3.16 μmol/kg, or 10 μmol/kg) during the initiation phase. A breakdown of the groups is as follows: group 1: saline + saline ($n = 12$); group 2: saline + methamphetamine (2.69 μmol/kg) ($n = 13$); group 3: PD144418 (3.16 μmol/kg) + saline ($n = 6$); group 4: PD144418 (3.16 μmol/kg) + methamphetamine (2.69 μmol/kg) ($n = 14$); group 5: PD144418 (10 μmol/kg) + saline; ($n = 7$) group 6: PD144418 (10 μmol/kg) + methamphetamine (2.69 μmol/

Table 1 Experiment 3-*intiation*

Groups	Days 1–5	Days 6–11	Day 12
1. Saline + saline	Saline + saline	No treatment	Saline + saline
2. Saline + methamphetamine	Saline + methamphetamine		Saline + methamphetamine
3. PD (3.16 μmol/kg) + saline	Saline + methamphetamine		Saline + saline
4. PD (3.16 μmol/kg) + methamphetamine	PD (3.16 μmol/kg) + saline		Saline + methamphetamine
5. PD (10 μmol/kg) + saline	PD (3.16 μmol/kg g) + methamphetamine		Saline + saline
6. PD (10 μmol/kg) + methamphetamine	PD (10 μmol/kg) + saline		Saline + methamphetamine

kg) ($n = 9$). On days 1–5, mice were placed in the activity monitor boxes for 45 min. After the 45 min, mice were administered either saline or PD144418 based upon their group. Fifteen minutes later, mice were administered methamphetamine or saline based upon their group. Over the next 7 days (days 6–11), animals remained in the colony room. On testing-day (day 12), mice were administered saline, followed by either saline or methamphetamine (2.69 μmol/kg). The effect of PD144418 on the induction of sensitization was analyzed using data from animals in the saline + saline, saline + methamphetamine, PD144418 + saline, and PD14418 + methamphetamine groups. For each analysis, data from days 1–5 were analyzed using a three-way RM-ANOVA, with day as the within-subject factor, and group and treatment as the between-group factors. The total distance traveled on day 12 was analyzed using a two-way ANOVA, with the dose of PD144418 and saline or methamphetamine as the between-subject factors. As in Exp. 1 and 2, a three-way RM-ANOVA was used to determine the effect of PD144418 on basal locomotor activity and methamphetamine-induced locomotor hyperactivity over 12 5-min increments. When appropriate ($p < 0.05$), a simple main effect analysis and post hoc comparisons, using a Bonferroni correction, were made.

Expression To assess the effects of PD144418 on the expression of methamphetamine sensitization (Table 2), mice ($n = 65$) were divided into six groups, of which three groups received saline + PD144418 challenge dose (0 μmol/kg, 3.16 μmol/kg, or 10 μmol/kg) after cessation, while the other three groups received methamphetamine (2.69 μmol/kg) + PD144418 challenge dose (0 μmol/kg, 3.16 μmol/kg, or 10 μmol/kg) after cessation. On days 1–5, mice were placed in the activity monitor boxes for 45 min. After the 45 min, mice were administered saline. Fifteen minutes later, mice were administered methamphetamine (2.69 μmol/kg) or saline. Over the next 7 days (days 6–11), animals remained in the colony room. On testing day (day 12), mice were administered either saline or PD144418 (3.16 μmol/kg or 10 μmol/kg) followed by either saline or methamphetamine (2.69 μmol/kg) based upon their group; group 1: saline + saline ($n = 11$); group 2: saline + methamphetamine (2.69 μmol/kg) ($n = 13$); group 3: PD144418 (3.16 μmol/kg) + saline challenge ($n = 9$); group 4: PD144418 (3.16 μmol/kg) + methamphetamine challenge (2.69 μmol/kg) ($n = 10$); group 5: PD144418 (10 μmol/kg) + saline challenge ($n = 10$); group 6 PD144418 (10 μmol/kg) + methamphetamine challenge (2.69 μmol/kg) ($n = 12$). Data from animals in the saline + saline, saline + methamphetamine, PD144418 + saline challenge, and PD144418 + methamphetamine challenge were used to analyze the effect of PD144418 on the expression of sensitization to methamphetamine. Similar to the analysis of the initiation of expression, a three-way RM-ANOVA was used to determine the effects on days 1–5, with day as the within-subject factor, and group and treatment as the between-group factor, and a two way-ANOVA was used to analyze the total distance traveled on day 12. Finally, a three-way RM-ANOVA was used to determine the effect of PD144418 on basal locomotor activity and methamphetamine-induced locomotor hyperactivity over 12 5-min increments. When appropriate ($p < 0.05$), a simple main effect analysis and post hoc comparisons, using a Bonferroni correction, were made.

Table 2 Experiment 3-*expression*

Groups	Days 1–5	Days 6–11	Day 12
1. Saline + saline	Saline + saline	No Treatment	Saline + saline
2. Saline + methamphetamine	Saline + methamphetamine		Saline + methamphetamine
3. PD (3.16 μmol/kg) + saline challenge	Saline + saline		PD (3.16 μmol/kg) + saline
4. PD (3.16 μmol/kg) + methamphetamine challenge	Saline + methamphetamine		PD (3.16 μmol/kg) + methamphetamine
5. PD (10 μmol/kg) + saline challenge	Saline + saline		PD (10 μmol/kg) + saline
6. PD (10 μmol/kg) + methamphetamine challenge	Saline + methamphetamine		PD (10 μmol/kg) + methamphetamine

Results

Experiment 1: acute effects of PD144418 on methamphetamine locomotor activity

The effects of PD144418 on basal locomotor activity and methamphetamine-induced locomotor hyperactivity for the 60-min period after methamphetamine or saline injections in male CD-1 mice are shown in Fig. 1. Figure 1a presents the total distance traveled for the 60-min period after methamphetamine or saline injections. As expected, there was a main effect of methamphetamine [$F(1,88) = 180.20$, $p < 0.001$], such that mice that received methamphetamine were more active than mice that received saline. Moreover, there was also a main effect of PD144418 dose [$F(3,88) = 121.70$, $p < 0.001$] and a PD144418 dose × methamphetamine interaction [$F(3,88) = 68.93$, $p < 0.001$]. First,a pairwise comparison using a Bonferroni correction

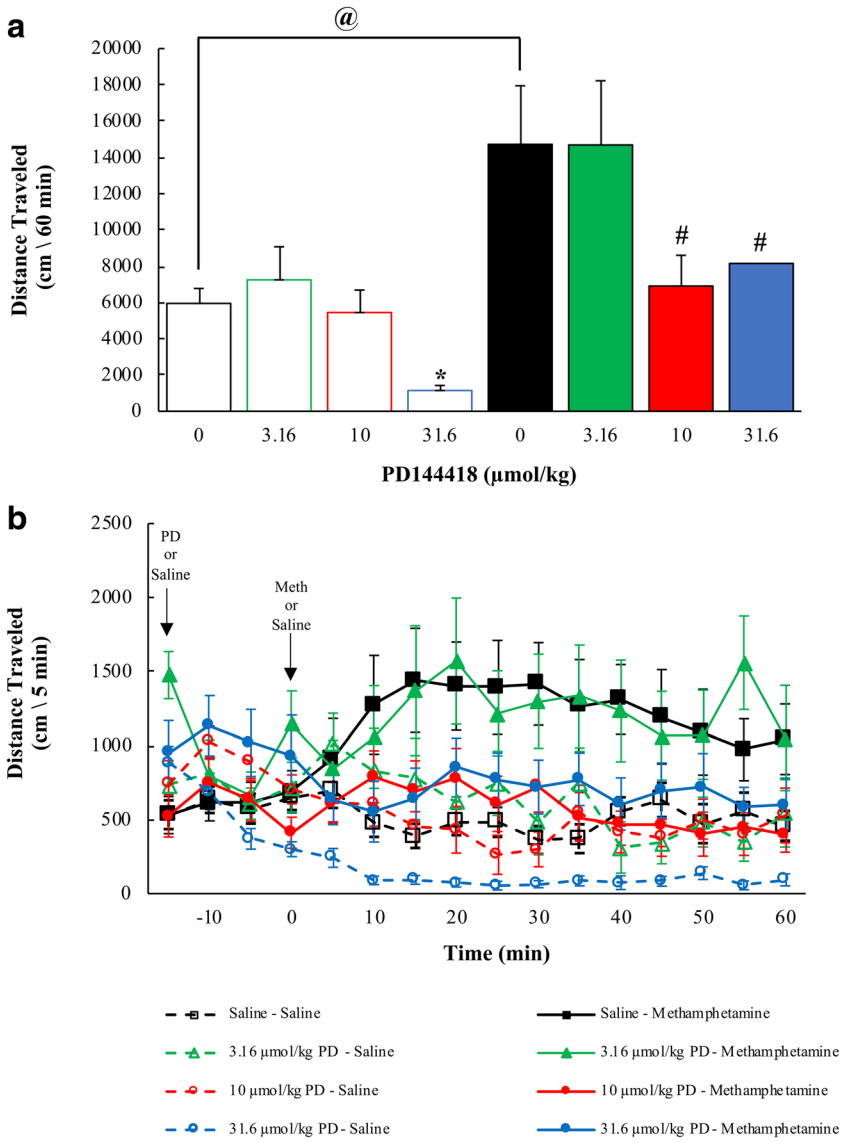

Fig. 1 Acute effects of PD144418 on methamphetamine locomotor activity. Data represented as mean ± S.E.M; $n = 8$–14 mice/group. Open symbols represent mice administered saline, and closed symbols represent mice administered methamphetamine. **a** Distance traveled (centimeters) over the 60-min period after administration of saline or methamphetamine (2.69 µmol/kg), by pretreatment with saline (0 µmol/kg) or PD144418 (3.16, 10, 31.6 µmol/kg). Group given saline followed by methamphetamine was more active than the group that received only saline (@) $p < 0.001$. Group given 31.6 µmol/kg PD144418 differed from the group given saline (*) $p < 0.001$; group given 10 or 31.6 µmol/kg PD144418 differed from group given methamphetamine, (#) $p < 0.001$. **b** Distance traveled (centimeters) in 5-min intervals over the 60-min period after administration of saline or methamphetamine (2.69 µmol/kg), by pretreatment with saline (0 µmol/kg) or PD144418 (3.16, 10, 31.6 µmol/kg). Arrows designate PD144418 or saline injection (time = − 15) and methamphetamine or saline injection (time = 0)

revealed an effect of methamphetamine, such that mice that received saline followed by methamphetamine were more active than mice that received only saline ($p < 0.001$). Moreover, post hoc analysis indicated that while PD144418 at the 3.16 and 10 μmol doses did not attenuate locomotor activity as compared to saline, at the high dose, mice administered 31.6 μmol PD144418 were less active than mice administered saline ($p < 0.001$). In regard to the effects of PD144418 on methamphetamine-induced locomotor activity, 10 μmol and 31.6 μmol of PD144418 attenuated methamphetamine-induced locomotor activity ($p < 0.001$).

The time course of the effects of PD144418 on basal locomotor activity and methamphetamine-induced locomotor hyperactivity over 12 5-min increments is presented in Fig. 1b. Results indicated main effects of PD144418 dose [$F(3,69) = 7.37$, $p < 0.001$], methamphetamine [$F(1,69) = 30.13$ $p < 0.001$], and time [$F(11,759) = 2.23$, $p < 0.001$]. A significant interaction of PD144418 dose × methamphetamine × time [$F(33,759) = 1.56$, $p < 0.05$] was also observed. Specifically, mice who received 10 μmol of PD144418 followed by methamphetamine were less active than mice administered saline followed by methamphetamine from the 25–50-min and 60-min time points ($p < 0.05$). Finally,

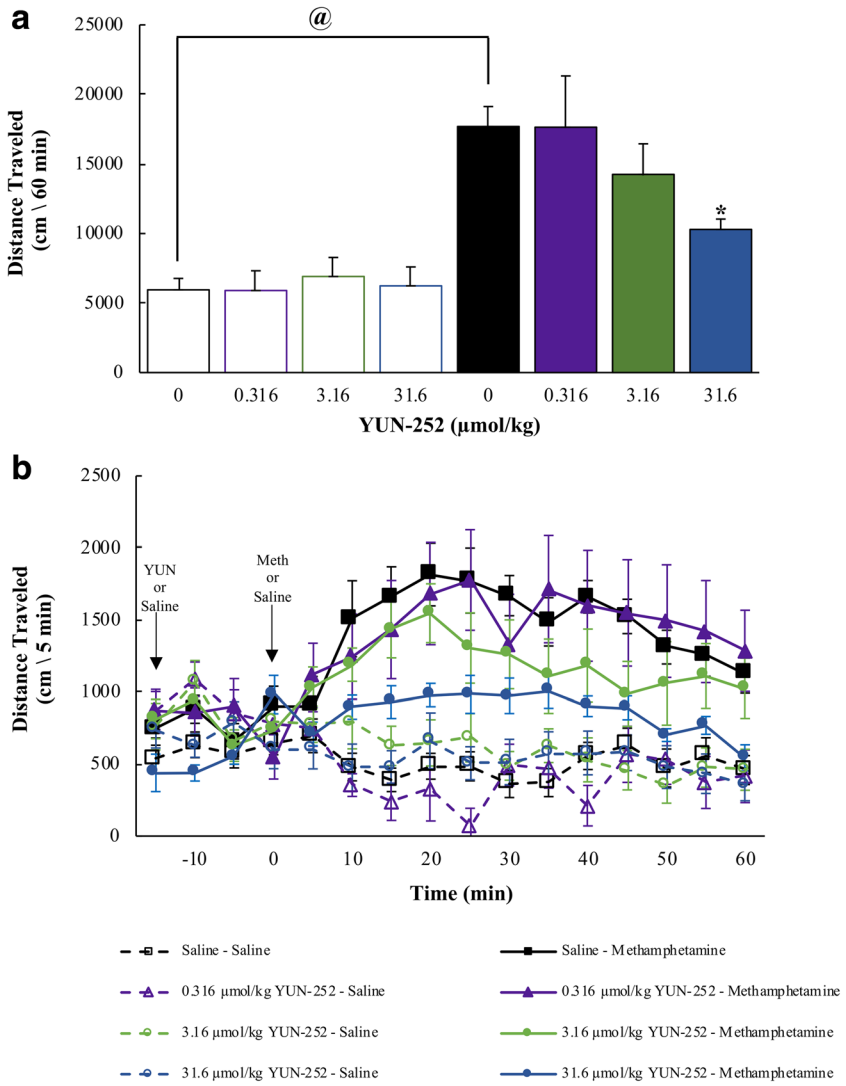

Fig. 2 Acute effects of YUN-252 on methamphetamine locomotor activity. Data represented as mean ± S.E.M; $n = 8$–14 mice/group. Open symbols represent mice administered saline, and closed symbols represent mice administered methamphetamine. **a** Distance traveled (centimeters) over the 60-min period after administration of saline or methamphetamine (2.69 μmol/kg), by pretreatment with saline (0 μmol/kg) or YUN-252 (0.316, 3.16, 31.6 μmol/kg, i.p.). Group given saline followed by methamphetamine was more active than the group that received only saline (@) $p < 0.001$. Group given 31.6 μmol/kg YUN-252 followed by methamphetamine differed from group given saline followed by methamphetamine, (*) $p < 0.001$. **b** Distance traveled (centimeters) in 5-min intervals after administration of saline or methamphetamine (2.69 μmol/kg), by pretreatment with saline (0 μmol/kg) or YUN-252 (0.316, 3.16, 31.6 μmol/kg). Arrows designate YUN-252 or saline injection (time = − 15) and methamphetamine or saline injection (time = 0)

31.6 μmol of PD144418 followed by methamphetamine significantly attenuated locomotor activity from the 40-min time point of the study as compared to mice administered saline followed by methamphetamine ($p < 0.05$).

Experiment 2: acute effects of YUN-252 on methamphetamine locomotor activity

The effects of YUN-252 on basal locomotor activity and methamphetamine-induced locomotor hyperactivity in male CD-1 mice are shown in Fig. 2. Figure 2a presents the total distance traveled for the 60-min period after methamphetamine or saline injections. Findings indicated a main effect of methamphetamine [$F(1,73) = 35.47$, $p < 0.001$], such that mice that received methamphetamine were more active than mice that received saline. Moreover, there was also a main effect of YUN-252 dose [$F(3,73) = 10.19$, $p < 0.001$] and a YUN-252 dose × methamphetamine interaction [$F(3,73) = 11.23$, $p < 0.001$]. Importantly, post hoc analysis revealed that mice that received saline followed by methamphetamine were more active than mice that received only saline ($p < 0.001$). Further analysis, using a Bonferroni correction, indicated that 0.316, 3.16, or 31.6 μmol of YUN-252 did not have an effect on locomotor activity as compared to saline ($p < 0.001$). In regard to methamphetamine-induced locomotor activity, there was an effect at 31.6 μmol of YUN-252, such that there was less activity for mice YUN-252 followed by methamphetamine than for mice administered saline followed by methamphetamine ($p < 0.001$).

As in Exp. 1, the time course of the distance traveled over 12–5-min increments is presented (Fig. 2b). Analysis indicated main effects of YUN-252 [$F(3,71) = 18.20$, $p < 0.001$], methamphetamine [$F(1,71) = 79.64$ $p < 0.001$], and time [$F(11,781) = 19.31$, $p < 0.001$]. However, YUN-252 × methamphetamine × time was not significant [$F(33,781) = 0.95$, $p = 0.51$].

Experiment 3: effect of PD14418 on methamphetamine sensitization

Initiation The effects of PD144418 on the initiation of locomotor sensitization to methamphetamine are presented in Fig. 3. Figure 3a depicts the initiation phase of methamphetamine sensitization, specifically the average total distance traveled for the 60-min period after the second injection of either methamphetamine or saline on days 1–5. Main effects of methamphetamine [$F(1,56) = 149.43$, $p < 0.001$] and PD144418 [$F(2,56) = 9.25$, $p < 0.001$] and an interaction of

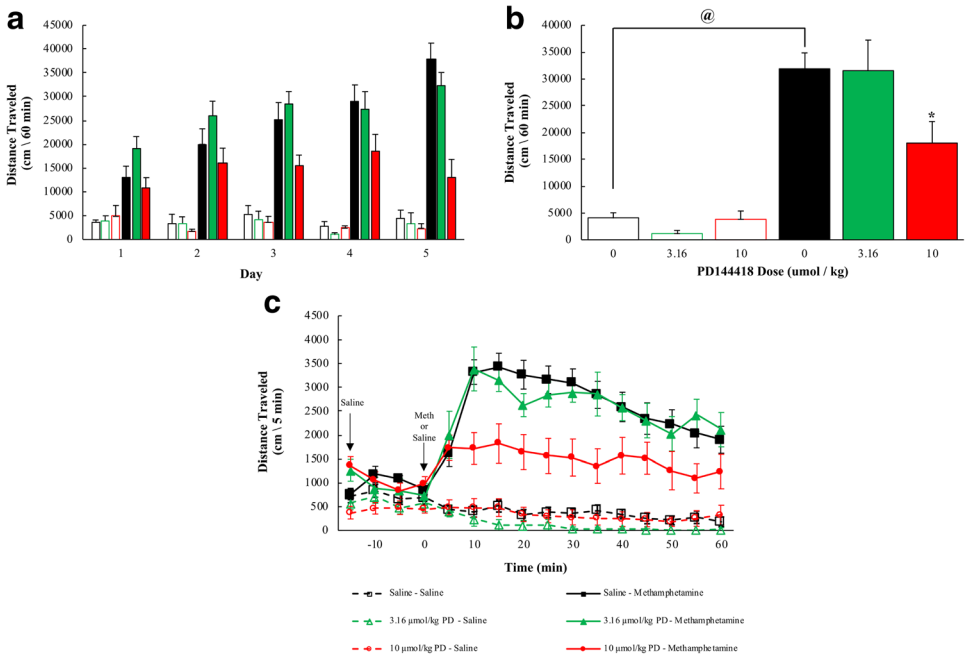

Fig. 3 Effects of repeated administration of PD144418 on locomotor-activating properties of methamphetamine. Data represented as mean ± S.E.M; $n = 7$–14 mice/group. Open symbols represent mice administered saline, and closed symbols represent mice administered methamphetamine. **a** Distance traveled (centimeters) over the 60-min period after administration of saline or methamphetamine (2.69 μmol/kg), by pretreatment with saline (0 μmol/kg) or PD144418 (3.16 or 10 μmol/kg) across treatment days (days 1–5). **b** Distance traveled (centimeters) over the 60-min period following administration of saline or methamphetamine (2.69 μmol/kg) on day 12. Group given saline followed by methamphetamine was more active than the group that received only saline (@) $p < 0.001$. Group given 10 μmol/kg PD144418 followed by methamphetamine differed from the group given saline followed by methamphetamine, (*) $p < 0.05$. **c** Distance traveled (centimeters) in 5-min intervals over the 60-min period after administration of saline or methamphetamine (2.69 μmol/kg), by pretreatment with saline (0 μmol/kg) or PD144418 (3.16 or 10 μmol/kg) on day 12. Arrows designate saline injection (time = − 15) and methamphetamine or saline injection (time = 0)

methamphetamine × PD144418 [$F(2,56) = 6.79$, $p < 0.001$] as expected were found. For the methamphetamine × PD144418 interaction, a significant decrease in locomotor activity was observed for mice that received 10 μmol/kg of PD144418 followed by methamphetamine as compared to animals that received only methamphetamine ($p < 0.001$) or 3.16 μmol/kg PD144418 followed by methamphetamine ($p < 0.001$). Moreover, while there was a main effect of day [$F(4,224) = 4.84$, $p < 0.001$] and a methamphetamine × day interaction [$F(4,224) = 6.27$, $p < 0.001$], such that locomotor activity increased for animals administered methamphetamine across the 5-day treatment period, PD144418 × methamphetamine × day [$F(8,224) = 1.45$ $p = 0.35$] was not significant. Therefore, PD144418 did not alter basal locomotor activity after repeated administration.

After 7 days of no drug treatment, animals were injected with either methamphetamine or saline on day 12. Figure 3b depicts the expression phase of methamphetamine sensitization. As expected, there was a main effect of methamphetamine [$F(1,54) = 135.94$, $p < 0.001$] and a trending effect of PD144418 dose [$F(2,54) = 2.67$, $p = 0.078$]. Analysis of PD144418 dose × methamphetamine indicated a significant interaction [$F(2,54) = 3.41$, $p < 0.05$]. Post hoc comparisons within the methamphetamine treatment groups indicated a decrease in locomotor activity between animals that received saline and animals that received 10 μmol/kg PD144418 ($p < 0.05$). Moreover, mice that received saline followed by methamphetamine were more active than mice that received only saline ($p < 0.001$). Thus, previous repeated pretreatment with PD144418 attenuated the locomotor response to an injection of methamphetamine, even in the absence of PD144418 pretreatment.

As with the previous experiments, the time course of the distance traveled over 12–5-min increments is presented in Fig. 3c. Results indicated mains effects of methamphetamine [$F(1,54) = 86.80$, $p < 0.001$], time [$F(11,781) = 4.61$ $p < 0.001$], and a trending effect of PD144418 [$F(2,54) = 2.67$, $p = 0.078$]. Significant interactions of PD144418 dose × methamphetamine [$F(2,54) = 3.41$, $p < 0.05$] and PD144418 dose × methamphetamine × time [$F(22,594) = 5.00$, $p < 0.001$] were also observed. Post hoc analysis indicated that there was less activity for mice who received 3.16 μmol of PD144418 followed by methamphetamine than for mice administered saline followed by methamphetamine at the 20-min time point ($p < 0.05$). A total of 10 μmol of PD144418 followed by methamphetamine significantly attenuated locomotor activity at the 10–50-min time points of the study as compared mice administered saline followed by methamphetamine ($p < 0.001$).

Expression The effects of PD144418 on the expression of locomotor sensitization to methamphetamine are presented

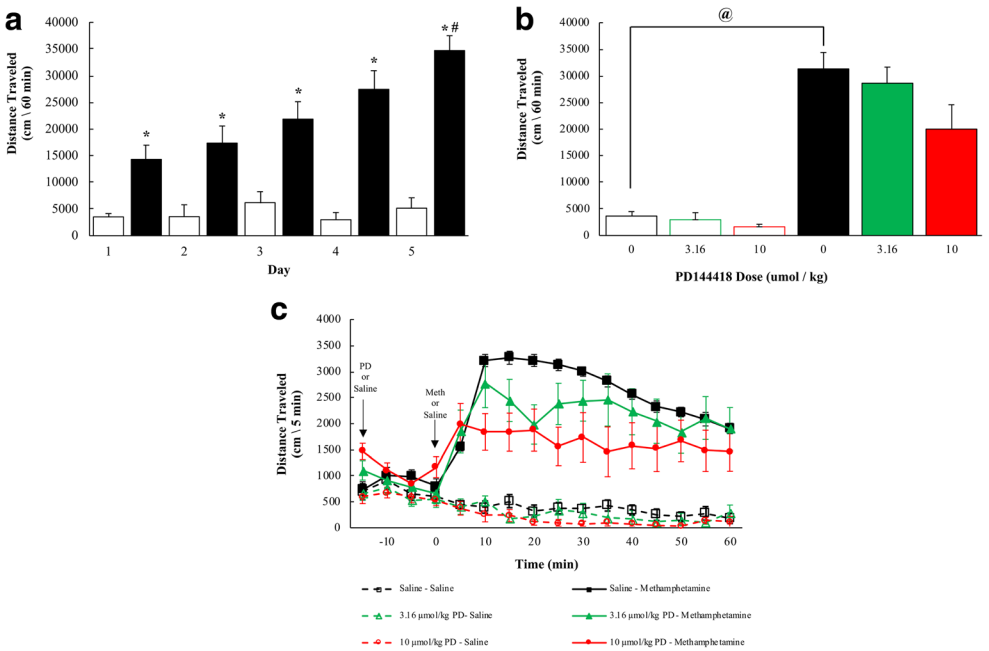

Fig. 4 Effects of PD144418 on the expression of sensitization to methamphetamine. Data represented as mean ± S.E.M; $n = 5$–14 mice/group. Open symbols represent mice administered saline, and closed symbols represent mice administered methamphetamine. **a** Distance traveled (centimeters) over the 60-min period after administration of saline or methamphetamine (2.69 μmol/kg) across treatment days (days 1–5). (*) $p < 0.001$ compared to saline; (#) $p < 0.001$ compared to days 1 and 2. **b** Distance traveled (centimeters) over the 60-min period after administration of saline or methamphetamine (2.69 μmol/kg), by pretreatment with saline (0 μmol/kg) or PD144418 (3.16 or 10 μmol/kg) on day 12. **c** Distance traveled (centimeters) in 5-min intervals over the 60-min period after administration of saline or methamphetamine (2.69 μmol/kg) on day 12. Arrows designate PD144418 or saline injection (time = − 15) and methamphetamine or saline injection (time = 0)

in Fig. 4. Figure 4a presents the initiation phase of methamphetamine sensitization, specifically the average total distance traveled for the 60-min period after the second injection of either methamphetamine or saline on days 1–5. Regarding repeated administration, methamphetamine significantly increased locomotor activity [$F(1,55) = 119.55, p < 0.001$] compared to animals who just received saline. Moreover, there was a significant interaction between methamphetamine and day [$F(4,55) = 4.16, p < 0.005$]. Post hoc tests determined that for animals treated with methamphetamine, activity was greater on day 5 than on days 1 and 2 ($p < 0.001$). Therefore, sensitization developed to the hyperactivity induced by 2.62 μmol/kg of methamphetamine.

After 7 days of no treatment, animals were injected with either saline or a PD144418 challenge dose on day 12. Figure 4b presents the expression phase of methamphetamine sensitization. Comparison of groups reviled a main effect of methamphetamine [$F(1,58) = 101.85$, $p < 0.001$], with post hoc comparisons indicating that mice that received methamphetamine were more active than mice that received saline ($p < 0.001$), and a trending effect of PD144418 dose [$F(2,58) = 2.83, p = 0.058$]. However, there was no interaction between PD144418 dose × methamphetamine [$F(2,58) = 1.48, p = 0.24$].

Finally, the time course of the distance traveled over 12–5-min increments on day 12 is presented in Fig. 4c. Main effects of methamphetamine [$F(1,58) = 95.81$, $p < 0.001$], time [$F(11,638) = 46.44$ $p < 0.001$], and a trending effect of PD144418 [$F(2,58) = 3.06, p = 0.055$] were observed. While there was not a significant interaction of PD144418 dose × methamphetamine [$F(2,58) = 1.29$ $p = 0.29$], there was a PD144418 dose × methamphetamine × time interaction [$F(22,638) = 1.69, p < 0.05$]. Post hoc analysis indicated that 10 μmol of PD144418 followed by methamphetamine significantly attenuated locomotor activity at the 10–40-min time points of the study as compared mice administered saline followed by methamphetamine ($p < 0.001$).

Discussion

The present study demonstrates that following acute administration, both PD144418 and YUN-252, in a dose-dependent manner, attenuated hyperactivity induced by an acute (0.5 mg/kg) methamphetamine injection. Moreover, repeated pretreatment with PD144418 attenuated hyperactivity in response to a methamphetamine challenge test dose, indicating that PD144418 attenuated the initiation of sensitization to methamphetamine. However, PD144418 does not appear to prevent the expression of sensitization to methamphetamine. It is important to note that the present data is only representative of male mice and conclusions are therefore limited by the fact that female mice were not assessed. There is clear evidence that sex differences exist for the influence of methamphetamine (Coughenour et al. 1977; Dluzen and Liu 2008; Roth and Carroll 2004; Ruda-Kucerova et al. 2015) and future studies will be required to address this issue.

In experiment 1, PD144418, in a dose-dependent manner, attenuated hyperactivity induced by an acute methamphetamine injection, such that mice that received 10 μmol/kg or 31.6 μmol/kg PD144418 followed by methamphetamine showed less activity than mice that received saline followed by methamphetamine. More importantly, treatment with 10 μmol/kg of PD144418 did not have an effect on basal locomotor activity. However, it should be noted that 31.6 μmol/kg of PD144418 did suppress basal locomotor activity. Suppression of basal locomotor activity at a higher dose is in line with previous research on PD144418 (Lever et al. 2014) and other σ_1 receptor antagonists (Kaushal et al. 2011; Sambo et al. 2017). One possible reason for such effects of PD144418 on basal locomotor activity at high doses includes alterations in brain regions involved in motor functioning, such as the cerebellum (Hayashi and Su 2005). Overall, these findings indicate that σ_1 receptors play a role in the locomotor-activating properties of methamphetamine. Moreover, results from these experiments are consistent with our previous research demonstrating that PD144418 attenuates cocaine-induced hyperactivity in mice (Lever et al. 2014). Additionally, the results are also in line with previous research of σ_1 ligands, BD1047 and BD1063, which at lower doses attenuated methamphetamine-induced hyperactivity in rodents, respectively (Lever et al. 2014; Nguyen et al. 2005; Sambo et al. 2017).

Examination of σ_2 receptor ligand YUN-252 resulted in an attenuation of hyperactivity induced by an acute methamphetamine injection. Specifically, mice that received the highest doses of YUN-252, 31.6 μmol/kg, followed by methamphetamine were less active than mice that received saline followed by methamphetamine. Importantly, YUN-252 did not have an effect on basal locomotor activity. Such results are consistent with previous research on the effects of YUN-252 (Lever et al. 2014) and other σ_2 receptor ligands (Kaushal et al. 2011; Matsumoto et al. 2007) on cocaine induce hyperactivity. Taken together, it indicates that σ_2 receptors play a role in the locomotor properties of psychomotor stimulants, including methamphetamine.

In addition to examining the acute effects of PD144418 on methamphetamine-induced hyperactivity, the effects of repeated administration of PD144418 in regard to methamphetamine sensitization were examined. At the highest dose, 10 μmol/kg, repeated administration of PD144418 not only attenuated methamphetamine-induced hyperactivity during the initiation phase itself, consistent with findings in experiment 1 but also phase prevented the development of methamphetamine sensitization, all while not having an effect on basal locomotor activity. These results are in line with previous

studies that examined other sigma receptor antagonists' effects on the development of methamphetamine sensitization (Kaushal et al. 2011; Ujike et al. 1992, 1996; Witkin et al. 1993). While the locomotor activity assay does not directly measure the rewarding or reinforcing properties of methamphetamine, the development of sensitization to psychomotor stimulants has been used to model the transition from drug "liking" to drug "craving" observed in humans (Wise and Bozarth 1987). Overall, the findings suggest that PD144418 may alter neuronal systems associated with the initiation of methamphetamine sensitization, as repeated methamphetamine administration to rodents usually leads to a stimulate-induced hyperactivity that persists through withdrawal periods (Robinson and Berridge 1993).

While PD14448 (10 μmol/kg) attenuated the development of methamphetamine-induced locomotor sensitization, such effects were not seen in regard to expression of sensitization to methamphetamine. Specifically, when animals were repeatedly treated with methamphetamine over a 5-day period, followed by a period of abstinence, PD144418 did not augment methamphetamine-induced locomotor activity. Interestingly, these results appear to differ from other sigma receptor antagonists' effects on the expression of methamphetamine sensitization (Kaushal et al. 2011; Xu et al. 2010). The differences observed in initiation and expression phases may be due to the fact that following a period of abstinence, or withdrawal, from psychomotor stimulants, there are changes in the expression of the dopamine and monoamine transporter genes in both the substantia nigra and the ventral tegmental area (VTA) (Li et al. 1997; Shilling et al. 1997). Moreover, withdrawal from psychostimulant drugs can lead to hypersensitivity of the mesolimbic dopaminergic systems (Vanderschuren and Kalivas 2000), in addition to an increase in accumbens dopamine release (Pierce and Kalivas 1997). Therefore, it may be that a dose of PD144418 larger than the ones selected is required to augment the expression of methamphetamine sensitization.

Though the mechanism by which PD144418 and YUN-252 acutely effect methamphetamine-induced behaviors is unknown, the proposed mechanisms by which the σ receptor and other σ receptor ligands work provide clues into potential mechanisms of the effects observed in the current study. For example, σ receptors can modulate neuronal firing and have been shown to affect the synthesis, release, and metabolism of neurotransmitters, including dopamine (Maurice et al. 2002, 2003; Navarro et al. 2010). Moreover, σ receptors have been shown to modulate dopaminergic functioning via the regulation of Ca^{2+} via inositol 1,4,5-trisphosphat (IP3) receptors on the endoplasmic reticulum (Derbez et al. 2002; Hayashi and Su 2004). Furthermore, methamphetamine exposure increases σ_1 levels in areas of the brain including the ventral tegmental area (VTA) and substantia nigra (Hayashi et al. 2010). An upregulation of σ_1 receptor levels has been shown to decrease methamphetamine stimulation of dopamine neurotransmission (Sambo et al. 2017). An increase in basal firing activity of dopaminergic neurons in the VTA can be blocked by σ_1 receptor antagonist rimcazole (Ceci et al. 1988). In regard to σ_2 receptors, studies that further address the involvement of the receptor subtype in regard to methamphetamine effects, such as sensitization, would be of value and provide clues as to the effects observed by YUN-252.

Overall, the current results suggest an intriguing potential for this novel sigma receptor ligand as a treatment for the addictive properties of methamphetamine. Future analysis of this novel sigma receptor ligand in assays directly measuring reinforcement properties will be critical.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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