



Do psychoactive drugs have a therapeutic role in compulsivity? Studies on schedule-induced polydipsia

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Received: 14 June 2017 / Accepted: 21 December 2017 / Published online: 8 January 2018
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Abstract

Rationale Clinical studies have shown that some psychoactive recreational drugs have therapeutic applications in anxiety, depression, and schizophrenia. However, to date, there are few studies on the therapeutic potential efficacy of recreational drugs in compulsive neuropsychiatric disorders.

Objectives We explored the therapeutic potential of different psychoactive and psychedelic drugs in a preclinical model of compulsive behavior.

Methods Outbred male Wistar rats were selected as either high (HD) or low (LD) drinkers according to their behavior in schedule-induced polydipsia (SIP). Subsequently, we assessed the effects of acute administration of scopolamine (0.125, 0.25, and 0.5 mg/kg), methamphetamine (0.25, 0.5, 1.25, and 2.5 mg/kg), ketamine (1.25, 2.5, 5, and 10 mg/kg), cannabidiol (1 and 3 mg/kg), WIN21255–2 (0.5, 0.75, and 1 mg/kg), and AM404 (0.25 and 0.5 mg/kg) on compulsive drinking in SIP.

Results Scopolamine reduced dose-dependent compulsive drinking in HD compared with LD rats in SIP. Methamphetamine induced a dose-dependent inverted U-curve effect in both groups, in which lower doses increased and higher doses reduced compulsive drinking in SIP. Ketamine, cannabidiol, WIN21255–2, and AM404 did not have any relevant effects in SIP.

Conclusions These data provide new evidence that low doses of scopolamine and intermediate doses of methamphetamine might therapeutically reduce compulsive behaviors and suggest that there is not a direct participation of the endocannabinoid system in compulsive behavior on SIP. The research in the underlying neurochemical mechanisms of these psychoactive drugs might provide an additional insight on new therapeutic targets in compulsive neuropsychiatric disorders.

Keywords Compulsivity · Schedule-induced polydipsia · Psychoactive drugs · Psychedelic drugs

Introduction

Compulsivity is associated with the loss of personal control over a broad range of behaviors that are prone to excess (Hollander et al. 2016). This condition is characterized by the performance of repetitive, undesirable, and dysfunctional acts without adaptive function, such as eating, gambling, and checking, according to rigid rules or to avoid negative consequences (Chamberlain et al. 2006; Fineberg et al. 2014). Compulsive behavior is typically observed in obsessive-compulsive disorder (OCD) and autism (Gillan et al. 2017; Kim et al. 2017) but has also been observed in many other neuropsychiatric disorders, such as

schizophrenia (de Haan et al. 2009; Swets et al. 2014), bipolar disorder (Amerio et al. 2014), anxiety (Agarwal et al. 2016), specific phobias (Torres et al. 2014, 2016), depression (Agarwal et al. 2016; Baer et al. 2015; Rickelt et al. 2016), and addiction (Fineberg et al. 2014). Compulsivity has different facets; indeed, some studies have supported a prognostic role for compulsivity in treatment outcome (Blanco et al. 2009; Grant et al. 2010; Ruehle et al. 2012). Reflecting the heterogeneity in compulsive symptoms, the treatment results are highly variable (Gillan et al. 2017). Pharmacological treatments for compulsivity are focused on antipsychotics and selective serotonin reuptake inhibitors (SSRI); however, up to 40% of patients do not respond successfully (Marinova et al. 2017). These facts motivate the exploration of new drugs that may have a therapeutic potential to reduce compulsive behavior.

In recent years, psychoactive drugs commonly used for recreational purposes, such as ketamine, scopolamine, methamphetamine, or cannabinoids, have aroused some interest

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because of their potential therapeutic applications. Previous studies have investigated the role of glutamatergic drugs in OCD (Marinova et al. 2017), in which ketamine remains an experimental treatment. Ketamine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist that modulates the glutamatergic system and exerts some effects on AMPA receptors, acetylcholine receptors, GABA receptors, μ -opioid receptors, and κ -opioid receptors, as well as inhibits the synaptic reuptake of noradrenaline and serotonin (Bruhn et al. 2017). In clinical studies, ketamine is a drug of interest because of its potential for a rapid onset of action, and administration of 0.5 mg/kg ketamine has shown antidepressant efficacy (Ionescu et al. 2014; Phelps and Brutsche 2009; Sos et al. 2013; Zarate et al. 2006), decreased suicidal ideations (Diazgranados et al. 2010) and anhedonia (Lally et al. 2014), and reduced symptomatology in posttraumatic stress disorder (Feder et al. 2014). Scopolamine is a non-selective muscarinic acetylcholine receptor (MACHR) antagonist that blocks the cholinergic function of the central nervous system by targeting muscarinic M1AChR and M2AChR receptors (Ionita et al. 2017). A single dose of scopolamine rapidly increases the spine number and function in layer V neurons, mTOR signaling, and glutamate release in the prefrontal cortex (Zarate et al. 2013). Scopolamine administration (4 μ g/kg) exhibited rapid antidepressant efficacy in patients with treatment-resistant depression (Furey et al. 2013) and induced anxiolytic effects in women (Furey et al. 2010). Methamphetamine (METH) is a psychostimulant drug, similar to D-amphetamine (Drug Enforcement Administration 2013; Wu et al. 2007), and exhibits potent full agonism of trace amine-associated receptor 1 (TAAR1), which increases cyclic adenosine monophosphate (cAMP) production and either completely inhibits or reverses the function of vesicular monoamine transporters for dopamine, norepinephrine, and serotonin (Cruickshank and Dyer 2009). METH also decreases the metabolism of monoamines by inhibiting monoamine oxidase, resulting in prolonged neuronal signaling (Cadet and Krasnova 2007; Krasnova and Cadet 2009). Although METH has become a major drug of abuse worldwide (Rau et al. 2016), it has been used for the treatment of weight control and depression as well as to increase alertness and prevent sleep (Drug Enforcement Administration, 2013). Recent studies have shown the therapeutic role of low doses of acute METH administration for neuroprotection in cognitive and behavioral impairment after severe traumatic brain injury (Rau et al. 2012, 2016).

Cannabinoid drugs exhibit effects via the cannabinoid receptors CB1 and CB2 (Russell 2017). The CB1 receptor is expressed in different brain areas, including those associated with impulsive-compulsive behaviors, such as the prefrontal cortex, striatum, and limbic system (Herkenham et al. 1991; Micale et al. 2009). In preclinical and clinical studies, cannabidiol (CBD) has demonstrated a broad range of potential therapeutic properties, such as antipsychotic, antidepressant, anxiolytic, antiepileptic,

sedative, and neuroprotective effects (Bergamaschi et al. 2011; Campos et al. 2016). Human studies on the exogenous cannabinoid AM404, an inhibitor of the fatty-acid amide hydrolase enzyme for endocannabinoid reuptake (Patel and Hillard, 2006), have reported anxiolytic properties and the attenuation of schizophrenia symptoms (Crippa et al. 2010; Leweke et al. 2012; Schubart et al. 2011; Zuardi et al. 1995). The full cannabinoid CB1 receptor agonist WIN55212-2 (Komaki et al. 2015) demonstrated neuroprotective effects on Parkinson disease (for a review, see More and Choi, 2011).

However, there are few preclinical and clinical studies on the therapeutic role of these psychoactive and psychedelic drugs on reducing compulsive behaviors in neuropsychiatric disorders. Schedule-induced polydipsia (SIP) model is characterized by the development of an adjunctive behavior of excessive drinking in food-deprived animals exposed to intermittent food-reinforcement schedules (Falk, 1961, 1966). The drinking response in SIP, considered as adaptive in nature, could serve as a coping or stress-reducing mechanism as indicated by reductions in plasma corticosterone levels (Brett and Levine, 1979; Dantzer et al. 1988a). Moreover, different studies have demonstrated relevant individual differences in SIP acquisition (Dantzer et al. 1988a,b; Mittleman et al. 1988). The excessive and persistent drinking response could indicate the development of a maladaptive compulsive behavior in SIP (Platt et al. 2008; Moreno and Flores, 2012). A similar phenomenon, known as psychogenic polydipsia, which includes compulsive non-regulatory fluid consumption, is present in 6–20% of psychiatric patients (de Leon et al. 1994, 2002; Dundas et al. 2007; Evenson et al. 1987; Iftene et al. 2013), and its treatment has shown a limited effectiveness (Greendyke et al. 1998; Delva et al. 2002). Different dopamine and serotonin agents such as antipsychotics and SSRIs efficiently reduce compulsive drinking on SIP (Íbias et al. 2016; for a review, see: Moreno and Flores, 2012; Platt et al. 2008). Moreover, the selection of high drinker (HD) and low drinker (LD) animals by SIP acquisition has shown that there are relevant behavioral and neurochemical differences. HD rats show lack of inhibitory control in 5-choice serial reaction time task (Moreno et al. 2012), latent inhibition deficit and cognitive inflexibility in reversal learning task (Navarro et al. 2016), and increased compulsive behavior in SIP after consuming tryptophan-depleted diet (Merchan et al. 2017) compared to LD rats. The administration of psychostimulant drugs, such as D-amphetamine and cocaine, as well as SSRIs, can efficiently reduce dose-dependent compulsive drinking behavior in HD rats in SIP (López-Grancha et al. 2008; Navarro et al. 2015). Indeed, administration of the serotonin 5-HT_{2A/C} receptor agonist DOI, a psychedelic drug, demonstrated a dose-dependent reduction of compulsive drinking in SIP for HD rats.

In the present study, we investigated the potential therapeutic role of psychoactive and psychedelic drugs that have

historically been used for recreational purposes in reducing compulsive drinking in a compulsive phenotype, the HD rats selected by SIP procedure. We explored the dose-response effects on compulsive drinking in two different groups of HD and LD rats. In the first group of HD and LD rats, we explored the effects of scopolamine, METH, and ketamine, and in the second group of HD and LD rats, we assessed the effects of acute administration of cannabinoid drugs, including cannabidiol, WIN55212-2, and AM404, on reducing compulsive drinking in SIP. The results are discussed in terms of the potential therapeutic effects of psychoactive and psychedelic drugs in a compulsive phenotype rat population and their implication as new pharmacological therapies for compulsive neuropsychiatric disorders.

Materials and methods

Subject

A total of 40 male Wistar rats (Janvier Labs, France) weighing approximately 250–350 g at the start of the experiments were used in the present study. The animals were housed four rats per cage (50 × 15 × 25 cm) at 22 °C, with a 12:12-h light-dark cycle (lights off at 08:00 h) and food and water provided ad libitum. Prior to SIP training and after 10 days of habituation, rats were gradually reduced to 85% of their free-feeding body weight through controlled feeding, and their body weights were maintained at this level of deprivation throughout the experiments. Food was provided daily at approximately 30 min after each experimental session. All testing was performed between 9:00 and 15:00 h. All procedures were performed according to the Spanish Royal Decree 1201/2005 on the protection of experimental animals and the European Community Council Directives (86/609/EEC).

SIP procedure

Rats were tested in eight operant SIP chambers (35 × 25 × 34 cm) (MED Associates, St. Albans, VT, USA). A detailed description of the apparatus has previously been provided (López-Grancha et al. 2008; Moreno et al. 2010). The scheduling and recording of experimental events were controlled using a computer and the commercial software Med PC (Cibertec SA, Spain). Over two successive days, a water ingestion test was conducted (baseline). Sixty pellets (Noyes 45-mg dustless reward pellets; TSE Systems, Germany) were placed together, and the amount of water consumed by each rat in 60 min was measured. After 1 day of adaptation, animals were exposed to a fixed time 60-s (FT-60s) schedule of food pellet presentation in 60-min sessions. Water bottles containing 100 ml of fresh water were provided during each session. After 20 daily sessions, animals were separated into two

specific populations, LD and HD, according to drinking rates (average for each animal over the last five sessions) above or below the group median, respectively. For the experimental drug studies, LD and HD rats were further divided into two subsequent groups according to their drinking rate: a first experimental group of HD ($n = 10$) and LD ($n = 10$) and second experimental group of HD ($n = 10$) and LD ($n = 10$). The following measures were recorded for each rat: (a) total amount of water (milliliters) removed from the bottle, (b) total number of licks on the bottle, and (c) total number of entries into the food magazine.

Experimental design

The behavioral effects of acute systemic administration of different drugs were tested in two separated groups of LD and HD rats in SIP. All animals received drugs according to a fully randomized Latin-square design, separated by a minimum of 72 h between drug test sessions and 15 days between different drug experiments (animals continued performing SIP sessions during these days). The experimental sessions were conducted on Tuesdays and Fridays, and baseline testing was performed on Mondays and Thursdays. On Wednesdays, animals performed the task, but the results were not analyzed. The experimental events are summarized in Fig. 1.

Experiment 1 We examined the effects of scopolamine, METH, and ketamine in LD and HD rats in SIP. The effects of scopolamine (0.125, 0.25, and 0.5 mg/kg), METH (0.25, 0.5, 1.25, and 2.5 mg/kg), and ketamine (1.25, 2.5, 5, and 10 mg/kg) were investigated in Group 1. The drug doses, injection time of approximately 30 min prior to behavioral testing and intraperitoneal (i.p.) administration, were implemented based on previous experiments (de la Peña et al. 2012; Petryshen et al. 2016; Refsgaard et al. 2017; Tizabi et al. 2012; Yamazaki et al. 2015).

Experiment 2 We explored the effects of CBD, WIN55212-2, and AM404 in HD and LD rats in SIP. We assessed the effects of the following drugs on SIP in group 2: CBD (1 and 3 mg/kg), WIN55212-2 (0.5, 0.75 and 1 mg/kg), and AM404 (0.25 and 0.5 mg/kg). The drug doses, injection time of approximately 30 min prior to behavioral testing, and intraperitoneal (i.p.) administration were selected based on previous experiments (Adameczyk et al. 2008; Campolongo et al. 2012; Espejo-Porras et al. 2013; Komaki et al. 2015; Zanelati et al. 2010).

Drugs

Scopolamine (scopolamine hydrobromide, (S)-3Hydroxy-2-phenylpropionic acid (1R,2R,4S,7S,9S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl ester), METH ((+)-

Fig. 1 Experimental procedure illustrated in a timetable. Drug doses were administered according to a fully randomized Latin-square design

SIP Procedure	Dose-response study (I)	(II)	(III)
Selection of HD and LD rats	Experiment 1: Scopolamine	METH	Ketamine
	Experiment 2: CBD	WIN-55212-2	AM-404

methamphetamine hydrochloride), and ketamine were dissolved in 0.9% saline. CBD ((-)-Cannabidiol), WIN55212-2 ((R)-(+)-WIN55212-2 mesylate salt), and AM404 (*N*-(4-hydroxyphenyl)-arachidonylamide) were suspended in 2% Tween-80 in 0.9% saline. All drugs were purchased from Sigma-Aldrich (Madrid, Spain), except CBD, which was purchased from Tocris Bio-Techne (Madrid, Spain). The injection volumes were 1 ml/kg for all drugs.

Data analysis

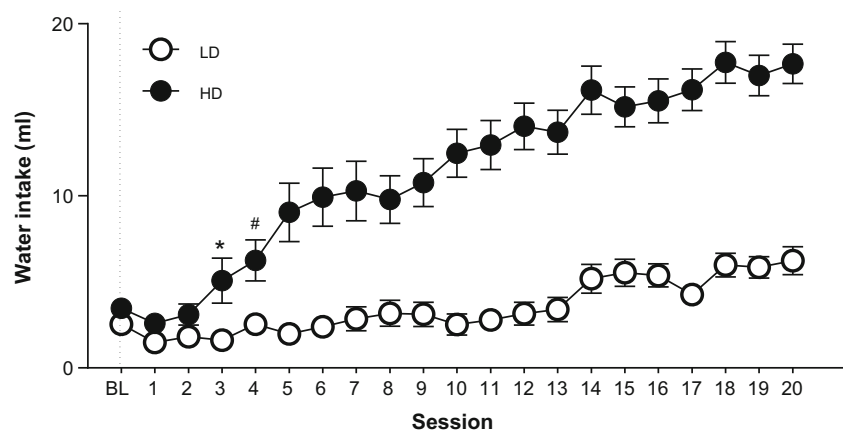
Behavioral data on SIP acquisition were analyzed using two-way repeated-measure analysis of variance (ANOVA), with “group” (LD and HD) as the between-subject factor and “sessions” (20 sessions) as the within-subject factor. The effects of the different drugs in LD and HD on SIP were analyzed using two-way repeated-measure ANOVA, with group (LD and HD) as the between-subject factor and “drug” (different doses of drug and vehicle) as the repeated within-subject factor. Post hoc comparisons were performed using the Newman-Keuls test. Statistical significance was set at $p < 0.05$. All analyses were computed using Statistica software (version 6.0).

Results

LD and HD selected by SIP

The mean water intake in LD and HD during acquisition and maintenance of SIP is shown in Fig. 2. In the experimental

Fig. 2 The mean (\pm SEM) water intake in FT-60s across 20 sessions of SIP. Statistical analyses indicate significant differences between high drinkers ($n = 20$) and low drinkers ($n = 20$) from that session onwards (asterisk). Significant differences from session 1 (number sign)



phase, the mean water intake over the last 5 days of SIP was 5.9 ± 0.1 and 16.6 ± 1.1 ml for LD and HD, respectively. The number of licks also showed SIP acquisition. The mean total licks averaged across the last 5 days of SIP were 763.4 ± 118.9 and 2296.6 ± 254.2 for LD and HD, respectively (data not shown).

ANOVA revealed significant differences in water intake according to the interaction between SIP acquisition sessions and LD vs. HD (interaction SIP session \times group effect: $F_{19, 722} = 14.56$, $p < 0.001$). This difference was also confirmed by the significant interaction observed in the total number of licks (interaction SIP session \times group effect: $F_{19, 722} = 6.79$, $p < 0.001$). Post hoc analysis indicated that the FT-60s schedule of food delivery induced different drinking rates across the 20 test sessions in both groups. Differences between the LD and HD animals were evident in the water intake at session 3 ($p < 0.05$) onwards. Furthermore, animals in the HD group significantly increased their consumption of water from session 4 ($p < 0.01$) compared to session 1. Differences between the LD and HD groups in the number of total licks at session 4 ($p < 0.01$) were also observed, and HD rats increased their number of licks from session 4 ($p < 0.05$) compared to session 1. There were no significant differences between LD and HD animals in the total magazine entries in SIP (data not shown).

Experiment 1. Effects of scopolamine, methamphetamine, and ketamine on SIP

The effects of scopolamine on water intake, total licks, and total magazine entries in SIP are shown in Fig. 3a and Table 1.

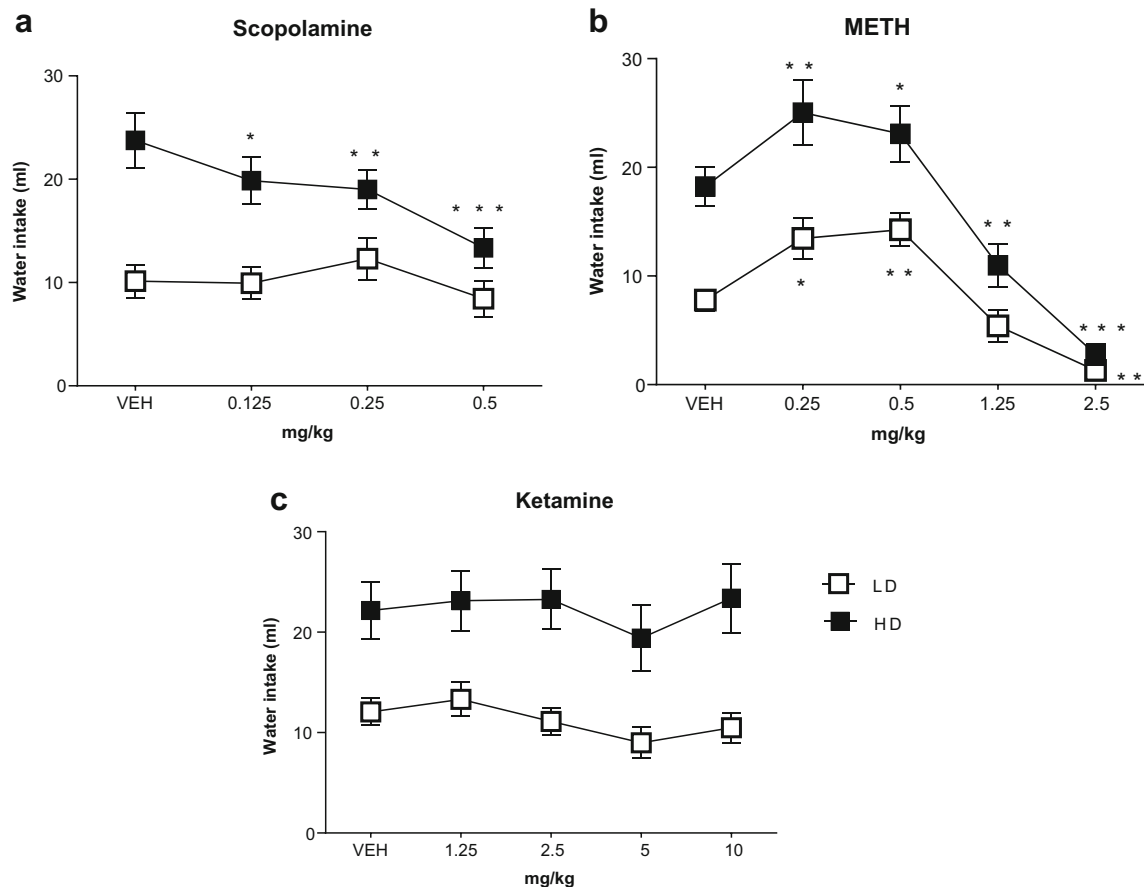


Fig. 3 Effects of **a** scopolamine, **b** methamphetamine METH, and **c** ketamine on the water intake of high drinkers (HD, $n = 10$) and low drinkers (LD, $n = 10$) rats in SIP. Data are expressed as the means \pm

SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ indicate significant differences versus vehicle administration in the same group of rats

Scopolamine significantly reduced compulsive water intake in HD rats compared to LD rats (group \times drug interaction, $F_{3, 54} = 6.24$, $p < 0.01$; group, $F_{1, 18} = 12.71$, $p < 0.01$; drug, $F_{3, 54} = 11.67$, $p < 0.001$). Post hoc analyses revealed that scopolamine reduced dose-dependent water intake in HD rats at the following doses: 0.125 ($p < 0.05$), 0.25 ($p < 0.01$), and 0.5 mg/kg ($p < 0.001$) compared with vehicle in the same group. Scopolamine did not affect water intake in LD rats. The comparison between LD and HD revealed a dose-dependent reduction of the significant differences in water intake (vehicle, $p < 0.001$; 0.5 mg/kg, $p < 0.05$). Moreover, scopolamine also significantly reduced the total licks in HD rats compared with the LD group (group \times drug interaction, $F_{3, 54} = 7.19$, $p < 0.001$; group, $F_{1, 18} = 7.02$, $p < 0.05$; drug, $F_{3, 54} = 7.72$, $p < 0.001$). Post hoc comparison confirmed a decrease in the total licks in the HD group at the highest dose used 0.5 mg/kg ($p < 0.01$) compared with vehicle in the same group. Differences between LD and HD remained significant at all doses tested. Scopolamine administration increased magazine entries in both groups of rats (group \times drug interaction, $F_{3, 54} = 2.55$, $p = 0.07$; group, $F_{1, 18} = 2.15$, $p = 0.16$; drug, $F_{3, 54} = 3.94$, $p < 0.05$). Post hoc analyses revealed an

increase in magazine entries in both groups only at the highest dose tested 0.5 mg/kg ($p < 0.05$) compared with vehicle.

The effects of METH on water intake, total licks, and magazine entries on SIP are shown in Fig. 3b and Table 1. METH significantly changed the water intake on SIP (group \times drug interaction, $F_{4, 72} = 4.35$, $p < 0.01$; group, $F_{1, 18} = 16.85$, $p < 0.001$; drug, $F_{4, 72} = 54.78$, $p < 0.001$). Post hoc analysis revealed that METH produced a dose-dependent U-inverted curve effect. The lower doses, 0.25 and 0.5 mg/kg, significantly increased water intake in both group of rats, LD ($p < 0.05$ and $p < 0.01$) and HD ($p < 0.01$ and $p < 0.05$), compared with vehicle in the same group. However, a higher dose of 1.25 mg/kg METH induced a different effect between HD and LD groups, whereas reduced water intake ($p < 0.01$) was observed in HD rats, and METH treatment did not affect the LD group ($p = 0.23$) compared with vehicle in the same group. This decrement in water intake in the HD group also revealed a reduction of the significant differences between HD and LD rats in water intake (vehicle, $p < 0.001$; 1.25 mg/kg, $p < 0.05$). At the highest dose used, 2.5 mg/kg METH significantly reduced water intake in both groups: LD ($p < 0.01$) and HD ($p < 0.001$) compared with vehicle in the same group. METH

Table 1 Effects of scopolamine, methamphetamine METH and ketamine on total licks and total magazine entries in high drinkers (HD, $n = 10$) and low drinkers (LD, $n = 10$) rats in SIP

	Total licks		Total magazine entries	
	LD	HD	LD	HD
Scopolamine				
Vehicle	1426.13 ± 234.84	3683.90 ± 558.51	2494.10 ± 313.65	1998.60 ± 300.36
0.125 mg/kg	1705.50 ± 233.91	3812.10 ± 655.54	2626.40 ± 306.50	1822.00 ± 237.68
0.25 mg/kg	2261.90 ± 409.05	3752.60 ± 603.03	2733.50 ± 303.17	2114.30 ± 253.27
0.5 mg/kg	1797.20 ± 299.24	2736.00 ± 568.89**	2651.30 ± 259.58	2406.60 ± 213.78
METH				
Vehicle	1201.83 ± 194.66	2613.10 ± 440.26	2304.43 ± 263.08	1792.60 ± 205.81
0.25 mg/kg	2346.00 ± 453.38 *	4398.40 ± 600.10**	2427.90 ± 358.74	1965.40 ± 338.13
0.5 mg/kg	2778.90 ± 336.17 **	3354.30 ± 554.01	2582.90 ± 324.97	2024.70 ± 289.04
1.25 mg/kg	614.600 ± 184.93	1310.40 ± 317.63**	2393.90 ± 317.75	1918.70 ± 229.95
2.5 mg/kg	113.800 ± 52.70	128.300 ± 51.66***	1475.00 ± 257.95	1267.00 ± 305.31
Ketamine				
Vehicle	2302.43 ± 443.22	3655.03 ± 614.47	2499.27 ± 444.81	1933.13 ± 301.73
1.25 mg/kg	3286.00 ± 651.03	4161.70 ± 604.48	2234.20 ± 272.50	2012.00 ± 314.03
2.5 mg/kg	2508.10 ± 538.97	4009.10 ± 675.20	2364.50 ± 320.81	1939.20 ± 266.07
5 mg/kg	1842.40 ± 459.14	3607.50 ± 674.76	1845.70 ± 298.42	1675.10 ± 249.92
10 mg/kg	2234.80 ± 381.77	4625.30 ± 633.06	2247.00 ± 366.47	1791.10 ± 225.94

Data are expressed as the means ± SEM

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ indicate significant differences versus vehicle administration in the same group of rats

significantly altered the total licks in SIP (group × drug interaction, $F_{4, 72} = 3.4$, $p < 0.05$; group, $F_{1, 18} = 7.28$, $p < 0.05$; drug, $F_{4, 72} = 51.02$, $p < 0.001$). Post hoc analyses showed that the lowest doses used (0.25 and 0.5 mg/kg) increased the total licks in the LD group ($p < 0.05$, $p < 0.01$, respectively) and a dose of 0.5 mg/kg increased the total licks in the HD group ($p < 0.01$) compared to vehicle in the same group. A dose of 1.25 mg/kg reduced the total licks only in the HD group ($p < 0.01$) compared with vehicle in the same group. The highest dose of METH reduced the total licks in the HD group ($p < 0.001$) and showed a decreasing trend in LD animals ($p = 0.06$) compared with vehicle in the same group. The comparison between the LD and HD groups showed that the dose of 1.25 mg/kg reduced the significant differences by decreasing the total licks response in the HD group (vehicle, $p < 0.05$; 1.25 mg/kg, $p = 0.24$). A drug effect via METH administration was observed in magazine entries in both groups (group × drug interaction, $F_{4, 72} = 0.21$, $p = 0.9$; group, $F_{1, 18} = 1.93$, $p = 0.18$; drug, $F_{4, 72} = 6.35$, $p < 0.001$). The post hoc comparison revealed a reduction in magazine entries in both groups only at the highest dose used 2.5 mg/kg ($p < 0.01$) compared with vehicle.

The effects of ketamine on water intake, total licks, and magazine entries in SIP are shown in Fig. 3c and Table 1. ANOVA showed that ketamine induced significant differences in water intake (group × drug interaction, $F_{4, 72} = 1.09$, $p = 0.37$; group, $F_{1, 18} = 11.64$, $p < 0.01$; drug, $F_{4, 72} = 5.22$, p

< 0.005), total licks (group × drug interaction, $F_{4, 72} = 1.69$, $p = 0.16$; group, $F_{1, 18} = 4.8$, $p < 0.05$ drug, $F_{4, 72} = 3.28$, $p < 0.05$), and magazine entries (group × drug interaction, $F_{4, 72} = 2.56$, $p = 0.69$; group, $F_{1, 18} = 0.88$, $p = 0.37$; drug, $F_{4, 72} = 2.57$, $p = 0.05$). Post hoc comparison revealed that only the 5-mg/kg dose reduced water intake ($p = 0.007$) and total magazine entries ($p = 0.04$) in both groups of rats compared with vehicle, while differences in total licks were only observed between drug doses in both groups but not between any doses compared to vehicle.

Experiment 2. Effects of cannabinoids on SIP

The effects of CBD on water intake and other behavioral measures in SIP are shown in Fig. 4a and Table 2. CBD induced non-selective slight reduction in water intake in both group of rats in SIP (group × drug interaction, $F_{2, 36} = 0.98$, $p = 0.98$; group, $F_{1, 18} = 13.34$, $p < 0.01$; drug, $F_{2, 36} = 3.26$, $p = 0.05$). Post hoc analysis showed that only the 1 mg/kg dose reduced the water intake ($p = 0.04$) in both group of rats. The measure of total licks showed a non-significant trend in response to CBD administration in SIP (group × drug interaction, $F_{2, 36} = 0.34$, $p = 0.71$; group, $F_{1, 18} = 13.21$, $p < 0.01$; drug, $F_{2, 36} = 2.98$, $p = 0.06$). The significant differences in water intake and total licks were maintained between HD and LD rats at all doses tested. There was also a drug effect following CBD administration in magazine entries in both groups of rats

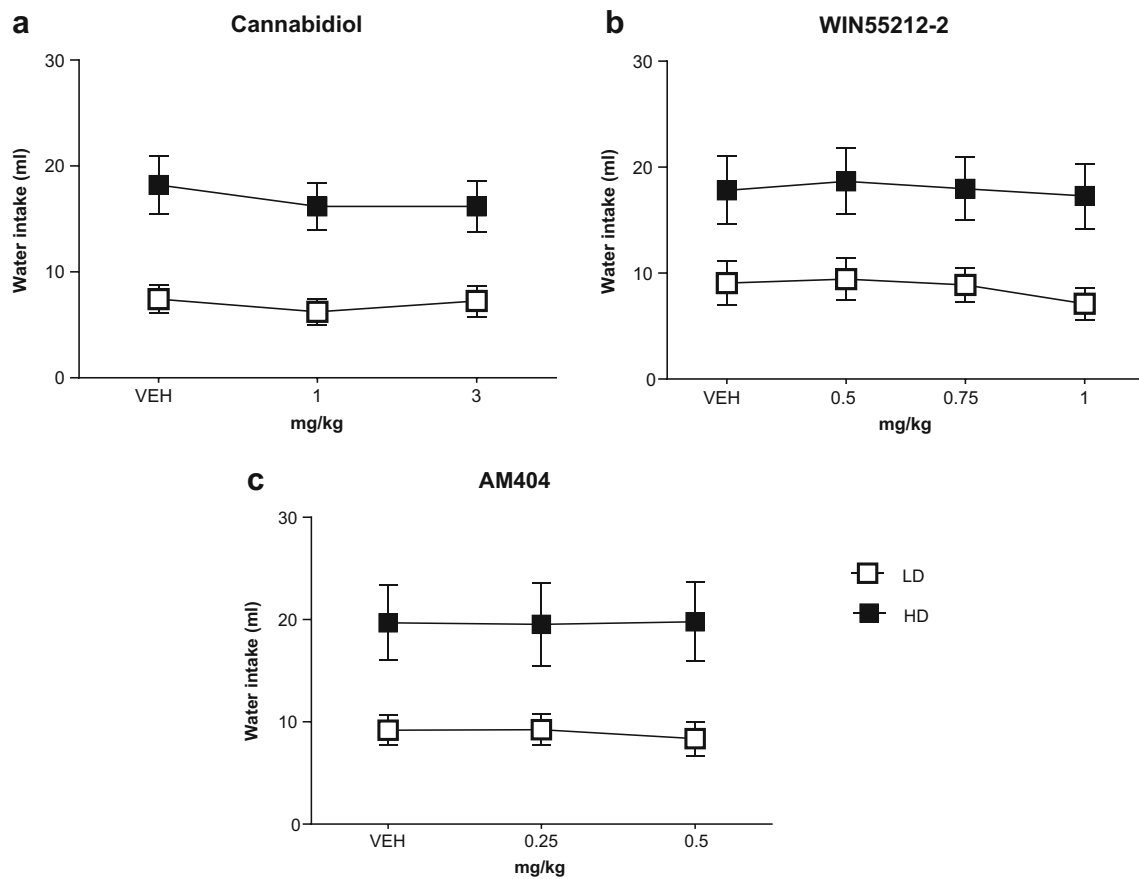


Fig. 4 Effects of **a** cannabidiol CBD, **b** WIN55212-2, and **c** AM404 on the water intake of high drinkers (HD, $n = 10$) and low drinkers (LD, $n = 10$) in SIP. Data are expressed as the means \pm SEM

(group \times drug interaction, $F_{2, 36} = 1.62, p = 0.21$; group, $F_{1, 18} = 0.66, p = 0.42$; drug, $F_{2, 36} = 4.03, p < 0.05$). Post hoc comparison revealed differences between CBD doses, but not compared with vehicle.

The effects of WIN-55212 on water intake, total licks, and total magazine entries in SIP are shown in Fig. 4b and Table 2. WIN-55212 did not produce significant effects on water intake in SIP (group \times drug interaction, $F_{3, 54} = 0.19, p = 0.90$;

Table 2 Effects of cannabidiol CBD, WIN55212-2, and AM404 on total licks and total magazine entries in high drinker (HD, $n = 10$) and low drinker (LD, $n = 10$) rats in SIP

	Total licks		Total magazine entries	
	LD	HD	LD	HD
Cannabidiol				
Vehicle	1107.73 \pm 253.09	2935.87 \pm 475.96	2418.50 \pm 164.01	2470.98 \pm 380.30
1 mg/kg	865.800 \pm 186.87	2549.10 \pm 338.60	1963.80 \pm 283.78	2568.40 \pm 488.38
3 mg/kg	1099.50 \pm 281.77	2716.00 \pm 460.44	2458.60 \pm 207.61	3071.40 \pm 639.39
WIN55212-2				
Vehicle	1382.50 \pm 400.33	3014.70 \pm 594.80	2575.70 \pm 234.56	2963.90 \pm 569.54
0.5 mg/kg	1370.50 \pm 332.74	2893.70 \pm 595.71	2387.30 \pm 242.34	2733.10 \pm 475.68
0.75 mg/kg	1361.30 \pm 284.64	2837.30 \pm 594.81	2508.40 \pm 253.00	2827.10 \pm 502.43
1 mg/kg	1148.70 \pm 337.09	2694.10 \pm 474.06	2705.60 \pm 216.66	2919.20 \pm 554.29
AM404				
Vehicle	1520.73 \pm 244.88	2948.63 \pm 507.79	2302.23 \pm 309.30	2973.83 \pm 431.20
0.25 mg/kg	1648.70 \pm 309.69	3186.40 \pm 480.08	2220.10 \pm 318.94	2809.20 \pm 508.01
0.5 mg/kg	1300.80 \pm 271.03	3266.60 \pm 592.79	2180.80 \pm 250.95	2966.30 \pm 460.76

Data are expressed as the means \pm SEM

group, $F_{1, 18} = 7.6, p < 0.05$; drug, $F_{3, 54} = 1.26, p = 0.30$). No significant effect was observed on the total licks in SIP (group \times drug interaction, $F_{3, 54} = 0.05, p = 0.98$; group, $F_{1, 18} = 6.35, p < 0.05$; drug, $F_{3, 54} = 0.67, p = 0.57$). The significant differences in water intake and total licks were maintained between HD and LD rats. No significant differences were observed in the magazine entries in SIP (group \times drug interaction, $F_{3, 54} = 0.17, p = 0.92$; group, $F_{1, 18} = 0.32, p = 0.32$; drug, $F_{3, 54} = 1.54, p = 0.22$).

The effects of AM404 on water intake, total licks, and total magazine entries in SIP are shown in Fig. 4c and Table 2. AM404 did not induce significant effects on water intake in SIP (group \times drug interaction, $F_{2, 36} = 0.73, p = 0.49$; group, $F_{1, 18} = 6.78, p < 0.05$; drug, $F_{2, 36} = 0.3, p = 0.74$). No significant effects were observed on the total licks in SIP (group \times drug interaction, $F_{2, 36} = 1.49, p = 0.24$; group, $F_{1, 18} = 8.44, p < 0.01$; drug, $F_{2, 36} = 0.66, p = 0.52$). AM404 did not affect magazine entries in SIP (group \times drug interaction, $F_{2, 36} = 0.3, p = 0.74$; group, $F_{1, 18} = 1.64, p = 0.22$; drug, $F_{2, 36} = 0.48, p = 0.62$).

Discussion

The present study investigated the potential therapeutic role of recreational psychoactive and psychedelic drugs in an animal model of compulsivity. The findings showed that scopolamine and METH administration altered compulsive drinking in SIP. In HD rats, which were characterized by excessive and persistent compulsive drinking in SIP, systemic administration of scopolamine reduced this behavior in a dose-dependent manner. Moreover, METH administration revealed an inverted U-curve effect via an increase at lower doses and decrease at higher doses of compulsive drinking in both groups of rats in SIP. Although 1.25 mg/kg METH revealed a decrease in compulsive water intake in HD rats, this treatment did not affect LD behavior. However, neither ketamine nor cannabinoid drugs administration induced selective effects on compulsive drinking in SIP as LD and HD maintained significant differences at all doses tested.

Scopolamine on compulsive drinking in SIP

The muscarinic acetylcholine MACHR antagonist scopolamine reduced dose-dependent compulsive drinking in HD rats via a reduction in water intake and total licks in SIP. Only the highest dose used reduced the number of magazine entries, indicating a possible modulation of food motivation (Pratt and Kelley, 2004). Our results are in agreement with those obtained by Sanger in 1976, where 1 mg/kg reduced SIP drinking in rats. However, the present results highlight the relevance of the effects of scopolamine at lower doses 0.125, 0.25, and 0.5 mg/kg, reducing SIP drinking in a

predisposed compulsive population, the HD compared the LD rats, selected by SIP. The present findings support a role for MACHR in the mechanisms underlying compulsive behavior in SIP. Scopolamine also reduces other compulsive behaviors, such as the perseverative behavior displayed in the marble-burying test (Broekkamp et al. 1986) and prevention of stereotypic augmentation (Ohmori et al. 1995). Other muscarinic MACHR antagonists, such as dicyclomine and tropicamide, reduce the activity of the muscarinic M1 receptor and modulate perseverative behavior by decreasing the number of marbles buried in the marble-burying test without producing sedative effects in wild-type animals and in a Fragile X syndrome mouse model (FXS), which is characterized by a wide spectrum of behavioral abnormalities (Veeraragavan et al. 2011a,b). Interestingly, cholinergic supersensitivity has been observed in patients with OCD (Lucey et al. 1993), and patients with fragile X syndrome frequently present symptoms of OCD (Feinstien and Reiss 1998; Hagerman 2002). Moreover, scopolamine can significantly increase the activity of acetylcholinesterase (AChE) levels in the cortex and hippocampus; and curiously in our laboratory, the acute exposure to chlorpyrifos (CPF), a common organophosphate (OP) insecticide whose primary mechanism of neurotoxic action is AChE inhibition, increased compulsive drinking on SIP (Cardona et al. 2006, 2011). Furthermore, scopolamine reduced the stress-induced corticosterone response in an animal model of depression (Katz and Hersh, 1981). Since corticosterone response is implicated in SIP (Dantzer et al. 1988a), this might be another important factor in the observed scopolamine dose-dependent reduction of compulsive drinking in HD animals on SIP. However, other studies have suggested that the muscarinic MACHR agonist oxotremorine methiodide is also effective in reducing compulsive behaviors in marble burying and self-grooming (0.001 and 0.01 mg) in a mouse model of autism (Amodeo et al. 2014). Therefore, altering cholinergic signaling through muscarinic receptors may provide a new therapeutic target for compulsive spectrum disorders and should be extensively investigated.

METH on compulsive drinking in SIP

The administration of METH, a monoamine transmission facilitator that inhibits the dopamine transporter involved in its reuptake, produces an inverted U-shaped dose-dependent effect on compulsive drinking in HD and LD rats in SIP. Thus, low doses (0.25 and 0.5 mg/kg) produced a significant increment, and the highest dose (2.5 mg/kg) reduced compulsive drinking in both groups compared with vehicle. The intermediate dose of 1.25 mg/kg only reduced compulsive water intake in HD rats, reducing the significant differences between HD and LD rats in SIP. In a previous study, we showed a decrease in compulsive drinking after administration of the psychoactive drugs D-amphetamine (0.5 and 1 mg/kg) and

cocaine (10 and 20 mg/kg) in SIP (Lopez-Grancha, et al. 2008). METH and D-amphetamine have a similar functional mechanism (Drug Enforcement Administration 2013; Wu et al. 2007). The present results of METH provide additional evidence to previous results of dopaminergic agents in reducing compulsive drinking on SIP (Íbias et al. 2016; for review see Moreno and Flores 2012). Consistent with these results, D-amphetamine (100 mg/kg) decreased the compulsive response of mice in the marble-burying test (Jimenez-Gomez et al. 2011). Previous studies have shown that METH administration (0.5, 1, and 2 mg/kg) reduced impulsive decision-making in a rat model, where rats choose between a delayed fixed (large) amount of water and immediate adjusted (small) amount of water (Richards et al. 1999). Other studies have also demonstrated the anxiolytic-like effects of METH administration (3 and 5 mg/kg) on increasing the time spent and distance traveled by rats in the open arm in the elevated plus maze (Tamaki et al. 2008; Xu et al. 2016). Recent evidence from preclinical and clinical studies indicate that METH under certain circumstances and correct dosing can produce a neuroprotective effect on cognition and neurogenesis after acute brain injury (for review see Rau et al. 2016).

Ketamine on compulsive drinking in SIP

We did not observe a selective effect via ketamine administration at any dose tested (1.25, 2.5, 5, or 10 mg/kg) on HD or LD rats in SIP, suggesting that NMDA receptors might not play a direct role in modulating compulsive behavior. Previous studies have demonstrated that ketamine administration induces dissociative dose-dependent effects; thus, rats receiving ketamine at 20 mg/kg/h showed dissociative behaviors (increased circling, reduced rearing, increased head weave, increased ataxia, and reduced grooming), while doses of 5 and 10 mg/kg/h reduced rearing and grooming (Radford et al. 2017). Acute (0.5–5.0 and 10 mg/kg i.p.) and chronic administration (0.5–2.5 mg/kg daily for 10 days) of ketamine resulted in a dose-dependent and prolonged decrease in immobility in the forced swimming test in rats, confirming the antidepressant-like effects of this drug (Refsgaard et al. 2017; Tizabi et al. 2012). Moreover, other studies have suggested the potential of ketamine to treat posttraumatic stress disorder, showing a decrease in freezing and anxious behaviors in rats and normalization of time spent in the aversive context after chronic ketamine administration (Zhang et al. 2015). In contrast, subchronic MK-801 administration, a potent NMDA antagonist, increased compulsive drinking in SIP (Hawken et al. 2011).

The role of cannabinoids on compulsive drinking in SIP

No significant effects on compulsive drinking were observed in HD and LD rats in response to acute AM404

and WIN55212-2 administration in SIP. CBD, at the dose of 1 mg/kg, induced a non-selective effect by a slight reduction of water intake and magazine entries in both groups in SIP. The results of the present study contrast with previous finding in which CBD, AM404, and WIN55212-2 have demonstrated therapeutic potential as antidepressive and anxiolytic drugs that reduce compulsive behavior in marble burying in rodent models. Different studies have demonstrated that acute administration of 15, 30, 60, and 120 mg/kg CBD (Casarotto et al. 2010; Deiana et al. 2012; Nardo et al. 2014) and 1 and 3 mg/kg WIN55212-2 and AM404 (Gomes et al. 2011) and intracerebroventricular injections of 0.05 µg/mouse (Umathe et al. 2011) reduced the compulsive behavior displayed in the marble-burying test in rodents. Cannabinoids also show an antipsychotic-like profile without inducing extrapyramidal-like effects, and 1 mg/kg WIN55212-2 increased the percentage of pre-pulse inhibition in spontaneously hypertensive rats, a model of schizophrenia (Levin et al. 2014). Self-administration of WIN55212-2 (290.5 ± 0.7 µg/kg) attenuated the psychotomimetic effects on phencyclidine-induced schizotypal symptoms in adult rats, such as hypermotility and the anxiety state (Spano et al. 2013; Umathe et al. 2012). At 15–60 mg/kg, CBD improved schizophrenic symptoms in rodents, inhibiting hyperlocomotion in the circular arena induced by psychotomimetic drugs (Moreira and Guimarães 2005). Moreover, at 1 and 3 mg/kg, WIN55212-2 and AM404 showed anxiolytic-like effects by increasing the time spent in the open arm of the elevated plus maze (Komaki et al. 2015; Patel and Hillard 2006). Furthermore, WIN55212-2 3 mg/kg administration improved decision choice strategies, increasing preferences for advantageous choices and decreasing disadvantageous choices in rats (Gueye et al. 2016). At 1 mg/kg, CBD produced beneficial effects in reversing the contextual fear-conditioning deficit displayed by spontaneously hypertensive rats (Levin et al. 2012). Acute administration of 30 mg/kg CBD; 0.2 mg/kg WIN55212-2; and 0.1, 0.3, 1, and 3 mg/kg AM404 induced therapeutic antidepressant-like effects in rats in the forced swim test (Adamczyk et al. 2008; Bambico et al. 2007; Biojone et al. 2011). Notably, although the interaction between the endocannabinoid and serotonergic systems plays a primordial role in the regulation of depressive and anxiety behaviors (Umathe et al. 2011), the cannabinoid drugs at the present doses did not induce a selective effect on compulsive drinking behavior displayed by HD rats in SIP. The present study could present a limitation in the doses used; however, they were chosen according to the literature (Adamczyk et al. 2008; Campolongo et al. 2012; Espejo-Porras et al. 2013; Komaki et al. 2015; Zanelati et al. 2010). Further studies should explore if any other doses or treatments with cannabinoid drugs

could induce a selective change in compulsive drinking behavior on SIP.

Conclusions

The present study is one of the first to assess the therapeutic potential of recreational psychoactive and psychedelic drugs in compulsive drinking behavior on SIP. The results of the present study showed the efficacy of the muscarinic acetylcholine receptor antagonist scopolamine to dose-dependently and selectively reduce compulsive drinking in HD rats in SIP. Blockade of muscarinic acetylcholine receptors could be of therapeutic interest according to previous data on reducing compulsive behaviors in an animal model of FXS. Administration of METH induced an inverted U-curve effect in compulsive drinking in both groups of rats in SIP. Therefore, the present results support the implication of muscarinic cholinergic system, like the dopamine and serotonin system, in the mechanisms of compulsive behavior in SIP. However, cannabinoid drugs did not show any therapeutic potential in the reduction of compulsive drinking in SIP. The lack of results from cannabinoid administration could reflect the different facets of compulsivity, in which the same treatment might show different results, highlighting different neurochemical mechanisms in the heterogeneity of compulsive behaviors. Future studies on the compulsive phenotype of HD rats in SIP could further identify new therapeutic pharmacological targets for compulsive neuro-psychiatric disorders.

Acknowledgements This work was supported by grants from the Ministerio de Economía y Competitividad, Spanish Government (grant number PSI2015-70037-R MINECO-FEDER).

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflicts of interest.

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