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ORIGINAL INVESTIGATION

Chronic cannabinoid exposure reduces phencyclidine-induced schizophrenia-like positive symptoms in adult rats

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Abstract
Rationale Chronic cannabis use can induce psychotic states that resemble schizophrenia. Yet, schizophrenic patients often smoke cannabis as a form of self-medication to counter the aversive symptoms of schizophrenia. We recently demonstrated an ameliorating effect of cannabinoid self-administration (SA) on negative and cognitive schizophrenia-like symptoms induced experimentally by the non-competitive *N*-methyl-D-aspartate receptor antagonist phencyclidine (PCP). Whether cannabinoid SA alleviates or exacerbates schizophrenia-like positive symptoms is still unclear.
Objectives This follow-up study aimed to evaluate the effect of self-administered cannabinoid on PCP-induced schizotypic positive symptoms in adult rats.
Methods Male rats were trained to self-administer either the cannabinoid CB1 receptor agonist WIN 55,212-2 (WIN; 12.5 μg/kg/infusion) or its vehicle (Veh) intravenously. The effects of acute and chronic intermittent intraperitoneal administration of PCP (2.5 mg/kg) on motor parameters were then tested in Veh-SA and WIN-SA.
Results Cannabinoid SA significantly attenuated the psychotomimetic effects of PCP exposure observed in control rats. Following acute PCP administration, WIN-SA animals displayed more frequent rearing and lower anxiety-like profile than Veh-SA rats. WIN-SA rats also exhibited lower behavioural sensitisation to chronic PCP treatment as demonstrated by reduced hyperlocomotion in response to an acute PCP challenge. In addition, parallel experiments performed in experimenter-administered rats that received WIN at comparable SA doses confirmed the ameliorating effects of cannabinoid exposure on PCP-induced schizotypic behaviours, indicating that motivational effects were not responsible for the ameliorative effects of cannabinoids.
Conclusions Our results indicate that cannabis may exert protective effects on positive schizotypic symptoms in adult animals such as hypermotility and anxiety state.

Keywords Cannabinoids · PCP · Schizophrenia · Self-administration · Psychosis · Locomotor activity · Anxiety · Comorbidity · Abuse

Introduction

The lifetime occurrence of substance use disorder among schizophrenic patients is close to 50 % (Regier et al. 1990), with high comorbidity in both first-episode (Van Mastrigt et al. 2004) and prodromal cases (Rosen et al. 2006). Along with nicotine, cannabis is one of the most frequently abused substances among schizophrenics (Jablensky et al. 1992; Menezes et al. 1996; Duke et al. 2001), followed by cocaine, hallucinogens and caffeine (Schneier and Siris 1987; Winklbaur et al. 2006). Although the relationship between psychosis and cannabis is still debated, the actual neurobiological mechanisms underlying this comorbid association are unknown.

The main psychoactive ingredient of cannabis, Δ9-tetrahydrocannabinol (THC), produces schizophrenia-like positive and negative symptoms in healthy individuals when acutely administered intravenously (D'Souza et al. 2005). The high rate of cannabis use in people with recurrent psychotic episodes has been interpreted as an attempt to self-medicate

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either the aversive symptoms, particularly negative symptoms (Bersani et al. 2002; Peralta and Cuesta 1992), or the side effects of antipsychotic medications (Verdoux et al. 2005).

We recently reported that rats previously trained to self-administer the cannabinoid CB1 receptor agonist WIN 55,212-2 (WIN) did not display disruption of prepulse inhibition of the acoustic startle reflex, short-term memory deficits, nor alterations in social behaviour typically induced by the allosteric *N*-methyl-D-aspartate antagonist phencyclidine (PCP; 1-[1-phenylcyclohexyl] piperidine) (Spano et al. 2010), indicating that cannabinoids can attenuate the PCP-induced behavioural abnormalities related to certain symptoms of schizophrenia. Notably, CB1 receptor antagonists reverse sensorimotor gating deficits induced by PCP (Ballmaier et al. 2007), while CB1 receptor gene disruption counteracts PCP-induced social deficits in mice (Haller et al. 2005), suggesting that the endocannabinoid system exerts differential effects on the many behavioural endophenotypes of schizophrenia. In keeping with these, it has been shown that THC attenuates hyperlocomotion induced by the psychostimulant dexamphetamine (Long et al. 2009).

Locomotor activation in rodents is thought to reflect the capacity of a drug to provoke psychosis in humans (Wolf 1998) and is used as a predictor of the propensity of a drug to elicit or exacerbate psychosis (Steinpreis et al. 1994; Adams and Moghaddam 1998). Repeated PCP administration induces hyperlocomotion and increases rearing and sniffing behaviours in mice and rats (Sturgeon et al. 1982; Nabeshima et al. 1987; Nagai et al. 2003). As antipsychotic drugs have been shown to reverse these PCP-induced motor responses (Freed et al. 1984; Kitaichi et al. 1995), repeated PCP administration has been widely recognised as an animal model of the positive symptoms of schizophrenia (Sturgeon et al. 1979; Nabeshima et al. 1983; Corbett et al. 1995; Sams-Dodd 1995, 1998; Mohn et al. 1999; Daenen et al. 2003). Altered emotional state is also a characteristic feature of schizophrenia, and schizophrenic patients are often diagnosed as suffering from anxiety-like disorders (Tibbo et al. 2003; Braga et al. 2004; Townsend and Wilson 2005). For this reason, along with ambulation, we evaluated the time spent by rats at the periphery of the locomotor activity cage, which is considered an index of the anxiety-like state (Gray 1979; Gentsch et al. 1987; Jinks and McGregor 1997; Cannizzaro et al. 2001). Thus, rather than attempting to model such a complex syndrome in its entirety, we used PCP to induce in rats potentially homologous behavioural phenomena that can be examined both in animals and in patients with schizophrenia.

Cannabinoid receptors are densely expressed in brain structures like the cerebellum and basal ganglia that are known to be critically involved not only in the initiation and coordination of movements (Breivogel and Childers 1998) but also in the pathogenesis of schizophrenia (Katsetos et al. 1997; Nicolás et al. 2011; Solowij et al. 2011). Animal studies indicated that acute treatment with THC or cannabidiol, a non-psychoactive component of *Cannabis sativa*, antagonises locomotor stimulation induced by amphetamine administration (Gorriti et al. 1999; Moreira and Guimanares 2005), whereas CB1 receptor blockade potentiates amphetamine-induced locomotor effects (Masserano et al. 1999). As the attenuation of amphetamine-induced hyperactivity implies an antipsychotic potential (Bruhwyler et al. 1990; Maj et al. 1996; Campiani et al. 1998; Ellenbroek and Liégeois 2003), these studies further support the involvement of the endocannabinoid system in the expression of psychotic behaviours.

At present, only few preclinical studies have used the PCP model of schizophrenia to investigate the effects of experimenter-given cannabinoids on animal motor activity (Pryor et al. 1977; Haller et al. 2005). In the present study, we examined the effect of voluntary intake of a low dose of the CB1 receptor agonist WIN on motor activity by combining the chronic intravenous self-administration (SA) procedure in rats (Fattore et al. 2001) and the PCP animal model of schizophrenia (Spano et al. 2010).

Animals were first trained to self-administer intravenously WIN (12.5 μg/kg/infusion) until drug intake was stable (Fattore et al. 2007; Spano et al. 2010). Phencyclidine was then administered either acutely or chronically, and different motor parameters, as well as anxiety-like behaviour, were compared between WIN-SA and vehicle-SA (control) groups. To rule out the possibility that the motivational drive to self-administer WIN contributes to the PCP-induced alterations in locomotor activity, we included a parallel group of rats passively treated with the cannabinoid, i.e. with WIN administered by the experimenter.

Materials and methods

Animals

Male Lister hooded rats (Harlan-Nossan, Milan, Italy), weighing 250–275 g at the beginning of the study, were used. Following arrival, animals were housed four/cage in a climate-controlled animal room on a reversed light/dark cycle (light on from 7:00 p.m.), with free access to water. Food was available ad libitum until the start of the experiments, during which it was moderately restricted (to 20 g/day) to maintain free feeding weights at ~85 %. Animals were handled by the experimenters for 1 week prior to testing. All experiments were approved by the local animal care committee and carried out in strict accordance with the European Commission regulations for animal use in research (CEE n° 86/609). All efforts were made to minimise animal suffering and reduce the number of animals used.

Drugs

For self-administration training and chronic (passive) treatment, WIN (Tocris, UK) was dissolved in one drop of Tween 80 and then diluted in heparinized (1 %) vehicle (0.9 % sterile saline solution); the volume of injection was 100 μl. In order to ensure sterility, the drug solution was passed through 22-μm syringe filters prior to use.

Phencyclidine hydrochloride (PCP; Sigma-Aldrich, UK) was freshly dissolved in sterile saline and administered intraperitoneally (i.p.) at 5 ml/kg. All antibiotics and anaesthetics were purchased as sterile solutions from local distributors.

Surgery

Following 1 week of acclimation, animals were deeply anaesthetized with Equithesin (0.97 g pentobarbital, 2.1 g magnesium sulphate, 4.25 g chloral hydrate, 42.8 ml propylene glycol, 11.5 ml ethanol 90 %, 5 ml/kgi.p.), and a permanent intravenous catheter (CamCaths, Cambridge, UK) was surgically implanted and secured to the right jugular vein as previously described (Fattore et al. 2001). After surgery, each rat was allowed to recover alone in its own home cage and received a daily intravenous infusion of gentamicin (0.16 mg/kg), followed by 0.2 ml of a heparinized (1 %) sterile saline solution to flush the antibiotic through the catheter. This treatment regime was maintained for 7 days.

Apparatus

Cannabinoid self-administration was performed in 12 operant chambers (29.5×32.5×23.5 cm), each encased in a sound- and light-attenuating cubicle equipped with a ventilation fan (Med Associates, USA). The front panel of the box contained two retractable levers (each 4-cm wide), positioned 12-cm apart and 8 cm from the grid, and extended 1.5 cm into the box. A white light stimulus (*cue*) was placed between the levers, and a dim red house light located on the opposite wall was kept on throughout the entire session. Each self-administration session started with the extension of the two levers into the operant chamber. Pressure to one lever (defined as active) resulted in a contingent infusion of WIN or vehicle (100 μl), while depression of the other lever (defined as inactive) was always recorded but had no programmed consequence. According to a continuous (FR-1) schedule of reinforcement, a single active lever press resulted in a drug infusion (over 5 s) and in the illumination of the white cue light for 5 s. Subsequently, a 15-s timeout period was introduced, during which time, both levers were retracted, and the white cue light was turned off.

WIN self-administration procedure

Daily training sessions of WIN (12.5 μg/kg/infusion) self-administration were conducted from Monday to Saturday (9:30 to 12:30 a.m.) under a continuous (FR-1) schedule of reinforcement and lever pressing as operandum, as previously described (Fattore et al. 2007, 2010). Acquisition training was carried out until steady baseline of drug intake was reached, i.e. when animals displayed accurate discrimination between the active and the inactive lever, with the number of active lever presses not differing by more than 20 % for four consecutive days. Animals were then allowed to continue SA training sessions for seven extra days (maintenance phase) (WIN-SA group; $n=7$) before undergoing PCP treatments. In parallel, a different set of animals were allowed to self-administer the vehicle (Veh) under the same experimental conditions. As expected, control rats (Veh-SA group; $n=7$) never acquired operant responding.

WIN chronic passive treatment

In a separate set of experiments, two groups of animals ($n=6$/group) received the passive treatment regimen. Either WIN (0.3 mg/kg, WIN-treated group) or vehicle (Veh-treated group) was administered by intravenous (i.v.) injection for 14 days. The WIN dose was selected based on past SA studies (Spano et al. 2010) in which the mean daily cannabinoid intake varied between 290.5±0.7 and 304±1.45 μg/kg. To mimic the self-administration pattern of drug intake, WIN was administered at the same rate of infusion (100 μl/5 s) twice daily, with a 1-h interval separating the two i.v. injections (Spano et al. 2010).

Experimental design and treatments

Once self-administration and chronic passive treatment phases were concluded; animals were divided into two main experimental groups and treated according to our previous study (Spano et al. 2010):

1. *Acute PCP administration*: animals received a single i.p. injection of PCP (2.5 mg/kg) or saline (Sal, 1 ml).
2. *Chronic intermittent* (*CHR*) *PCP administration*: animals received i.p. injections of PCP (2.5 mg/kg) or Sal (1 ml) on days 1–5, 8, 10, 12, 15, 17, 19, 22, 24 and 26, for a total of 14 injections.

Locomotor activity testing

Rats were individually tested for locomotor activity under standardised environmental conditions using the Digiscan Animal Activity Analyser (Omnitech Eletronics, USA). Each operant cage (42×30×60 cm) was equipped with

two sets of 16 photocells located at right angles to each other, projecting horizontal infrared beams 2.5-cm apart and 4-cm above the cage floor and a further set of 16 horizontal beams which height could be adapted to the size of the animals. Locomotor activity was performed in a dark room dimly illuminated by a red lamp.

Animals were habituated for 1 h to the motility cage, then injected i.p. with either saline (1 ml) or PCP (2.5 mg/kg), and motor activity was monitored for an additional 60 min (test period). Locomotor activity testing took place twice, the first following *acute* Sal or PCP injection and then on the last day of the *chronic* treatment. The following behavioural parameters were measured:

Ambulation	the total horizontal distance travelled (cm).
Vertical activity	the total number of beam interruptions that occurred in the vertical sensors.
Margin time	the time(s) spent by the animal within 1 cm of the cage wall.

These parameters were recorded every 10 min for 60 min, beginning immediately after the animal was placed in the cage. The arena was wiped out with 70 % ethanol between sessions to prevent olfactory cues.

Statistical analysis

For locomotor activity in acute experiments, data were compared by one-way ANOVA. If a significant difference was detected, the Newman–Keuls multiple comparison test was carried out as a post hoc test to compare individual means. The unpaired Student's *t* test was used to compare the effect of treatments (PCP vs Sal) between all paired groups (Veh-SA vs WIN-SA; Veh-treated vs WIN-treated rats). Finally, two-way ANOVA was used to compare self-administration groups versus passive treated groups.

For locomotor activity following chronic Sal or PCP administration under an acute challenge, data were compared using a two-way ANOVA (challenge × treatment). If a statistical significance was detected, the Bonferroni post hoc test was used for individual mean comparisons. One-way ANOVA was used to compare the effect of treatments in all groups. Statistical significance was set at $P<0.05$.

Results

In accordance with our previous studies (Fattore et al. 2007, 2010; Spano et al. 2010), animals took at least 2 weeks to acquire cannabinoid self-administration behaviour, and within the third week of training, they stabilise their drug intake at a mean of 290.5±0.7 μg/kg (average over the last 3 days of self-administration training).

Locomotor activity: acute treatment

Distance travelled

Figure 1 (*top*) shows the cumulative ambulatory distance (in centimetres) of animals that self-administered the cannabinoid agonist (WIN-SA, *black*) or vehicle (Veh-SA, *white*) in response to an acute injection of saline (1 ml) or PCP (2.5 mg/kg). Comparison of data from WIN-SA and Veh-SA groups did not show a main effect, as animals did not differ in their ambulation ($P>0.05$). A similar scenario is observed, following a saline or PCP challenge in animals passively injected by the experimenter with the cannabinoid (WIN-treated, *stripped*) or vehicle (Veh-treated, *grey*) (Fig. 1, *bottom*). Indeed, in Veh- and WIN-treated rats, an acute treatment of saline or PCP had no effect on distance travelled ($P>0.05$).

When comparing self-administration groups (top) versus passive treated groups (bottom), two-way ANOVA yielded neither treatment ($F_{1,44}=0$; $P=0.9097$) or group ($F_{3,44}=1.90$; $P=0.14.58$) effects, nor a significant group × treatment interaction ($F_{3,44}=0.51$; $P=0.6778$).

Vertical activity

As illustrated in Fig. 2 (top), acute PCP administration dramatically reduced vertical activity compared to acute saline in both

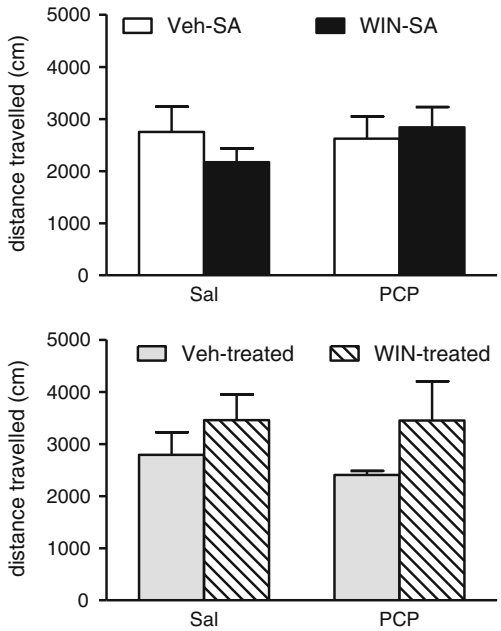

Fig. 1 Effect of acute PCP (2.5 mg/kg, i.p.) administration on distance travelled (in centimetres). *Top* animals self-administering vehicle (Veh-SA, *white*) or the cannabinoid agonist (WIN-SA, *black*) ($n=7$/group). *Bottom* animals passively administered with vehicle (Veh-treated, *grey*) or with the cannabinoid agonist (WIN-treated, *stripped*) ($n=6$/group). Each value represents the mean ± SEM of total locomotor activity during 60 min of observation (test period)

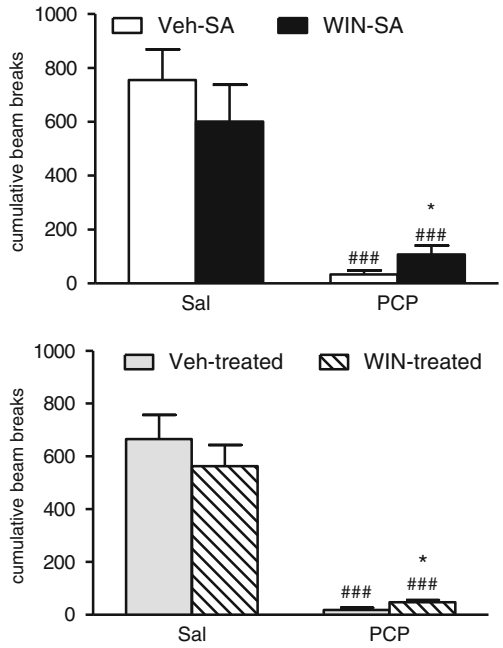

Fig. 2 Effect of acute PCP (2.5 mg/kg, i.p.) administration on vertical activity. *Top* animals self-administering vehicle (Veh-SA, *white*) or the cannabinoid agonist (WIN-SA, *black*) (n=7/group). *Bottom* animals passively administered with vehicle (Veh-treated, *grey*) or with the cannabinoid agonist (WIN-treated, *stripped*) (n=6/group). Each value represents the mean ± SEM of cumulative beam breaks during 60 min of observation (test period). *P<0.05 versus corresponding Veh group; ###P<0.001 versus corresponding control (Sal) group

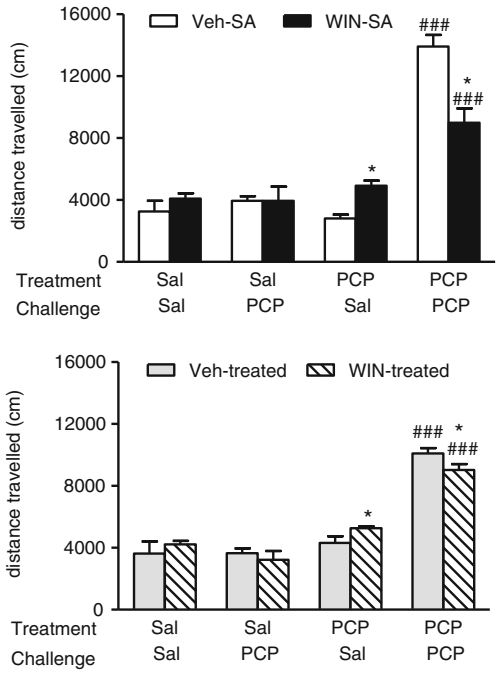

Fig. 3 Effect of chronic PCP (2.5 mg/kg, i.p.) administration on distance travelled (in centimetres). *Top* animals self-administering vehicle (Veh-SA, *white*) or the cannabinoid agonist (WIN-SA, *black*) (n=7/group). *Bottom* animals passively administered with vehicle (Veh-treated, *grey*) or with the cannabinoid agonist (WIN-treated, *stripped*) (n=6/group). Saline (*Sal*) or PCP was injected as a challenge on the last day of chronic treatment. Each value represents the mean ± SEM of total locomotion counts during 60 min of observation (test period). *P<0.05 versus corresponding Veh group; ###P<0.001 versus corresponding control (Sal) group

Veh-SA (white) and WIN-SA (black) rats (P<0.001), an effect that is significantly attenuated (P<0.05) in the WIN-SA group. Similarly, when the cannabinoid was passively injected (Fig. 2, bottom), PCP administration markedly decreased rearing in both Veh-treated (grey) and WIN-treated (stripped) rats (P<0.001), but the effect was more pronounced (P<0.05) in the Veh-treated than in the WIN-treated group.

When comparing self-administration groups (top) versus passive treated groups (bottom), two-way ANOVA detected a main effect of acute treatment ($F_{1,44}$=97.36; P<0.0001), but not a group effect ($F_{3,44}$=0.38; P=0.775), nor a significant group × treatment interaction ($F_{3,44}$=0.81; P=0.4938).

Locomotor activity: chronic treatment

Distance travelled

Figure 3 (top) illustrates the effects of acute saline (1 ml) and PCP (2.5 mg/kg) challenges on Veh-SA (white) and WIN-SA (black) rats treated chronically with either saline or PCP. In both SA groups chronically treated with saline (*left bars*), a challenge with saline or PCP had no effect on distance travelled. Conversely, following chronic PCP treatment (*right bars*), WIN-SA rats challenged with saline were hyperactive as compared with their Veh-SA counterparts (P<0.05). Notably, an acute PCP challenge evoked significant hyperactivity in both SA groups relative to saline challenge (P<0.001), with a significantly (P<0.05) greater stimulatory response in Veh-SA than in WIN-SA animals, implying that WIN self-administration partially attenuated the hyperlocomotion induced by acute PCP. Two-way ANOVA detected a main effect of challenge (PCP vs Sal, $F_{3,48}$=36.67; P<0.0001) and a significant challenge × treatment interaction ($F_{3,48}$=5.96; P<0.005), but not a significant effect of treatment ($F_{1,48}$=0.62; P=0.4343).

Figure 3 (bottom) depicts the effects of saline (1 ml) and PCP (2.5 mg/kg) challenges on Veh-treated (grey) and WIN-treated (stripped) rats passively injected chronically with saline or PCP. Following chronic treatment with saline (left bars), neither acute challenge with Sal or PCP altered ambulatory distance in vehicle- and WIN-treated rats. On the other hand, after chronic PCP treatment (right bars), WIN-treated rats were slightly more active than their Veh-treated counterparts, following a challenge with saline (P<0.05). An acute PCP challenge induced hyperlocomotion (P<0.001) in rats chronically treated with PCP, an effect that was less evident (P<0.05) in WIN-treated than in saline-treated rats, confirming the attenuating effect of WIN treatment on the hyperlocomotion induced by the

PCP challenge. Two-way ANOVA revealed a main effect of challenge ($F_{3,40}$=80.47; P<0.0001), but not a treatment effect ($F_{1,40}$=0; P=0.972), nor a significant challenge × treatment interaction ($F_{3,40}$=2.2; P=0.103).

Notably, when comparing self-administration groups (top) versus passive treated groups (bottom), two-way ANOVA revealed a main effect of treatment (PCP vs. Sal, $F_{3,88}$=125.06; P<0.0001) and a significant group × treatment interaction ($F_{9,88}$=6.35; P<0.0001), but not a significant effect of group ($F_{3,88}$=0.84; P=0.4752).

Vertical activity

Figure 4 (top) illustrates the effects of acute saline (1 ml) and PCP (2.5 mg/kg) challenges on Veh-SA (white) and WIN-SA (black) rats treated chronically with either saline or PCP. Cumulative data from saline-treated animals did not show significant dissimilarity between Veh-SA and WIN-SA rats. As compared with a saline challenge, in these animals, an acute challenge with PCP significantly reduces

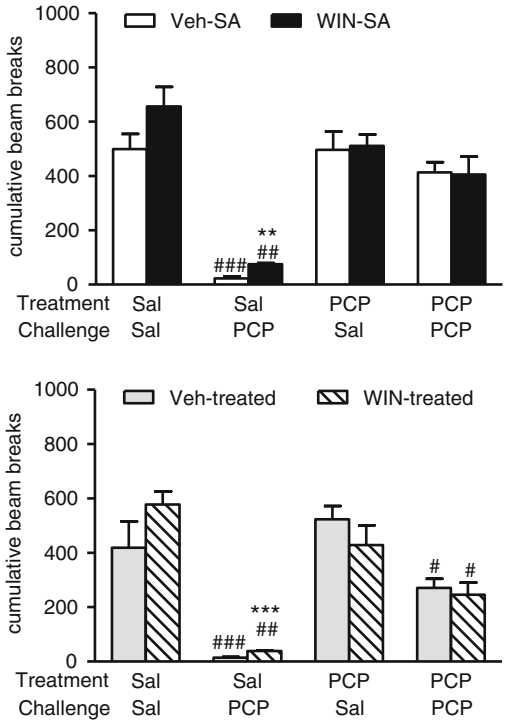

Fig. 4 Effect of chronic PCP (2.5 mg/kg, i.p.) administration on vertical activity. *Top* animals self-administering vehicle (Veh-SA, *white*) or the cannabinoid agonist (WIN-SA, *black*) (n=7/group). *Bottom* animals passively administered with vehicle (Veh-treated, *grey*) or with the cannabinoid agonist (WIN-treated, *stripped*) (n=6/group). Saline (*Sal*) or PCP was injected as a challenge on the last day of chronic treatment. Each value represents the mean ± SEM of cumulative beam breaks during 60 min of observation (test period). #P<0.05 versus corresponding PCP/Sal group; ###P<0.001 and ##P<0.01 versus corresponding control (Sal) group; ***P<0.001 and **P<0.01 versus corresponding Veh group

the number of rearings in both SA groups (P<0.01), an effect more evident in Veh-SA than in WIN-SA group (P<0.01). Conversely, chronic PCP did not impair vertical activity in either Veh-SA or WIN-SA rats, as both groups exhibited similar responses to acute saline or PCP challenge. Two-way ANOVA revealed a main effect of acute challenge ($F_{3,48}$= 21.55; P<0.0001), but not a chronic treatment effect ($F_{1,48}$= 2.24; P=0.1424), nor a significant challenge × treatment interaction ($F_{3,48}$=0.71; P=0.5511).

Figure 4 (bottom) depicts the effects of saline (1 ml) and PCP (2.5 mg/kg) challenges on Veh-treated (grey) and WIN-treated (stripped) rats chronically injected with saline or PCP. Similar to SA groups, an acute PCP challenge significantly (P<0.001) reduced rearing in both Veh-treated and WIN-treated animals chronically injected with saline (left bars), although to a lesser extent in the latest group. On the other hand, after chronic PCP administration, an acute challenge with saline did not impair vertical activity in either Veh- or WIN-treated rats, while these two groups showed a similar significant (P<0.05) decrease in rearing upon acute PCP challenge. Two-way ANOVA yielded a main effect of challenge ($F_{3,40}$=34.76; P<0.0001), but not a main treatment effect ($F_{1,40}$=0.19; P=0.6655), nor a significant challenge × treatment interaction ($F_{3,40}$=2.08; P=0.1186).

When comparing self-administration groups (top) versus passive treated animals (bottom), two-way ANOVA revealed a main effect of treatment ($F_{3,88}$=72.33; P<0.0001) and group ($F_{3,88}$=3.06; P<0.05), but not a significant group × treatment interaction ($F_{9,88}$=1.42; P=19.4). Thus, an acute PCP challenge markedly reduced rearing not only in Veh-SA and WIN-SA rats (top) but also in Veh- and WIN-treated rats (bottom) after chronic saline treatment and, to a lesser extent, in Veh- and WIN-treated rats (bottom) chronically injected with PCP.

Time spent on margins: acute treatment

Table 1 illustrates the cumulative peripheral activity of rats that self-administered the cannabinoid (WIN-SA) or its vehicle (Veh-SA) and that of rats passively injected with the CB1 agonist (WIN-treated) or its vehicle (Veh-treated) in response to acute saline or PCP injection.

Veh-SA rats showed significantly higher basal peripheral activity than WIN-SA animals (P<0.05), revealing a greater level of anxiety-like behaviour. As compared to corresponding control (Sal) groups, peripheral activity was significantly (P<0.05) increased in both Veh-SA (+30 %) and WIN-SA (+56 %) groups following acute PCP injection. Correspondingly, Veh-treated animals displayed significant (P<0.05) basal higher margin time activity than WIN-treated rats, as they spent most of the time on the margins of the cage, evocative of a higher level of anxiety-like behaviour. Conversely, following acute PCP administration, both groups of animals displayed

Table 1 Effects of acute Sal (1 ml) and PCP (2.5 mg/kg, i.p.) administration on peripheral activity in Veh-SA (n=7), WIN-SA (n=7), Veh-treated (n=6) and WIN-treated (n=6) rats

Acute injection		
	Sal	PCP
Self-administration		
Veh-SA	2,561±251	3,323 ±118*
WIN-SA	1,447±190**	2,257±348**, *
Passive treatment		
Veh-treated	1,821±117	2,814±55*
WIN-treated	1,488±109**	2,613±108*

Each value represents the mean ± SEM of time on margins (in seconds) during 60 min of observation

*P<0.05, versus corresponding control (Sal) group; **P<0.05, versus corresponding Veh group

significant (P<0.05) higher margin time activity than the control (Sal) group (Veh-treated rats, +54 %; WIN-treated rats, +75 %). Following acute drug treatment, two-way ANOVA yielded a main effect of treatment ($F_{1,44}$=35.21; P<0.0001) and group ($F_{3,44}$=9.31; P=0.775), but not a significant group × treatment interaction ($F_{3,44}$=0.29; P=0.8316).

Time spent on margins: chronic PCP

Table 2 shows the cumulative peripheral activity of rats that self-administered the cannabinoid (WIN-SA) or its vehicle (Veh-SA) and that of rats passively injected with the CB1 agonist (WIN-treated) or its vehicle (Veh-treated) in response to chronic saline or PCP injection.

Following chronic saline treatment (top, *left*), Veh-SA and WIN-SA rats showed different basal peripheral activities (P<0.001), in line with acute administration data. Notably, even following a PCP challenge, Veh-SA animals displayed a more anxious profile than WIN-SA rats (P<0.01), as demonstrated by their higher peripheral activity. In contrast, in Veh-SA animals treated chronically with PCP (top, *right*), no statistically significant differences were detected between rats challenged with saline or PCP, suggesting the absence of anxiety-related behavioural traits. Intriguingly, following chronic PCP treatment, WIN-SA rats displayed a significantly decreased (P<0.05) margin time activity with respect to Veh-SA animals following saline or PCP challenges. Indeed, peripheral activity was lower than following chronic saline treatment for both SA groups. Two-way ANOVA revealed a main effect of challenge ($F_{3,48}$=13.35; P<0.0001) and treatment ($F_{1,48}$=31.23; P<0.0001), but not a significant challenge × treatment interaction ($F_{3,48}$=1.60; P=0.2038).

Similarly, following chronic saline treatment (bottom, left), Veh- and WIN-treated rats challenged with Sal showed different basal peripheral activities (P<0.001), while no statistically significant differences were detected in both groups of animals challenged with PCP, suggesting the absence of anxiety-related traits. However, WIN-treated animals showed a significantly higher (P<0.05) level of anxiety than the corresponding control (Sal) group. Finally, following chronic PCP treatment (bottom, right), WIN-treated rats challenged with either Sal (P<0.001) or PCP showed significantly decreased (P<0.05) margin time activity with respect to Veh-treated animals. Two-way ANOVA revealed a main effect of challenge ($F_{3,40}$=20.13; P<0.0001) and treatment ($F_{1,40}$=27.12; P<0.0001), but not a significant challenge × treatment interaction ($F_{3,40}$=2.54; P=0.069).

When comparing self-administration groups (top) versus passive treated animals (bottom), two-way ANOVA revealed a main effect of treatment ($F_{3,88}$=31.59; P<0.0001) and group ($F_{3,88}$=21.53; P<0.05), but not a significant group × treatment interaction ($F_{9,88}$=1.01; P=0.44).

Table 2 Effect of chronic Sal (1 ml) and PCP (2.5 mg/kg, i.p.) administration on peripheral activity in Veh-SA (n=7), WIN-SA (n=7), Veh-treated (n=6) and WIN-treated (n=6) rats

CHR treatment	Sal		PCP	
Challenge	Sal	PCP	Sal	PCP
Self-administration				
Veh-SA	2135±126	2,971±222*****	1,742±106	1,543±128
WIN-SA	952±138***	1,968±271**, ****	851±325*	1,013±145*
Passive treatment				
Veh-treated	2,020±136	2,364±235	1,633±104	1,382±163
WIN-treated	1,019±108***	2,232±261****	819±135***	857±127*

Sal or PCP was injected as a challenge on the last day of chronic treatment. Each value represents the mean ± SEM of time spent on margins (in seconds) during 60 min of observation

P<0.001, **P<0.01 and *P<0.05 versus corresponding Veh group; *****P<0.01,*P<0.05 vs corresponding control (Sal) group

Discussion

We have recently demonstrated that cannabinoid self-administration attenuated the cognitive and negative schizotypic behaviours induced by PCP in adult rats (Spano et al. 2010). In this follow-up study, we used the same PCP animal model to evaluate the effects of the CB1 receptor agonist WIN on behavioural endophenotypes of the positive symptoms of schizophrenia. There are several difficulties associated with modelling schizophrenia in animals; as heterogeneity in clinical symptoms, course of the disorder and potential contributing factors represent considerable obstacles. Yet, the PCP model has been proved to possess face and predictive validity, although construct validity remains tricky to ascertain, as with other animal models of schizophrenia (Marcotte et al. 2001).

The present findings demonstrated that cannabinoid self-administration partially, but significantly, ameliorated the psychotomimetic motor effects induced by acute and chronic intermittent PCP administration. In particular, the main results of the present study were threefold. Firstly, following chronic PCP treatment, WIN-SA animals displayed baseline hyperactivity but reduced expression of behavioural sensitisation to PCP, as compared to Veh-SA rats. Secondly, rearing behaviour (as measured by vertical activity) was greatly reduced, following acute PCP in both self-administration groups, but to a lesser extent in WIN-SA rats than in Veh-SA counterparts. Finally, cannabinoid self-administration causes a reduction in anxiety-like behaviour under both basal condition and following PCP treatment. These results are in line with our earlier findings revealing an intriguing role for the endocannabinoid system in ameliorating PCP-induced behavioural impairments in prepulse inhibition of acoustic startle, cognitive skills and sociability (Spano et al. 2010), indicating that cannabinoid agonists can attenuate PCP-induced schizotypic behavioural abnormalities.

In humans, positive symptoms generally refer to a loss of contact with reality and consist of severe hallucinations, delusions, bizarre behaviours and psychomotor agitation characterised by hyperactivity and stereotypic movements. Exposure to chronic PCP has been reported to mimic certain aspects of schizophrenia in healthy human subjects and to worsen symptoms in schizophrenic patients (Turner and Tsuang 1990; D'Souza et al. 2000; Nunn et al. 2001; Skosnik et al. 2001; Degenhart et al. 2007). In laboratory animals, PCP induces hyperactivity and stereotyped behaviour that respond to treatment with typical and atypical antipsychotics (Javitt and Zukin 1991; Murray and Horita 1979), which validated its use as a reliable animal model of schizophrenia (Jentsch and Roth 1999; Moghaddam and Jackson 2003; Morris et al. 2005).

In the present study, no difference in ambulation was observed after acute PCP administration. In chronically PCP-treated rats, however, an acute PCP challenge induced a robust increase in ambulation in both Veh- and WIN-SA rats. Notably, WIN-SA rats exhibited a smaller increase in ambulation than Veh-SA rats, indicating that cannabinoid self-administration attenuated PCP-induced behavioural sensitisation. Behavioural sensitisation, characterised by a progressive and enduring enhancement in the motor response elicited by an acute drug challenge after repeated exposure to a drug, has been implicated in both drug addiction (Vanderschuren and Kalivas 2000) and psychosis (Duncan et al. 1999; Yui et al. 1999). Noteworthy, repeated administrations of PCP have been shown to result in behavioural sensitisation upon PCP challenge (Xu and Domino 1994; Johnson et al. 1998). Whatever the precise role of the endocannabinoid system in modulating schizophrenia-like motor behaviours, it is acknowledged that cannabinoids affect motor activity through CB1 receptors, which are abundant in brain structures related to motor control, such as basal ganglia and cerebellum (Herkenham et al. 1991; Mailleux and Vanderhaeghen 1993; Matsuda et al. 1993), by regulating glutamatergic and GABAergic systems within these same neuronal networks (Rodríguez de Fonseca et al. 1998; Fernández-Ruiz and Gonzáles 2005).

Yet, we observed a different scenario when measuring vertical activity. In line with earlier studies (Krebs-Thomson et al. 1998; Hori et al. 2000; Krebs-Tang et al. 2006), acute PCP administration dramatically decreased vertical activity in both self-administration groups, although the effect was significantly greater in Veh-SA than in WIN-SA rats. Differently from ambulation, rearing did not undergo behaviour sensitisation upon chronic PCP treatment, as rats chronically treated with PCP did not change their rearing activity after either saline or PCP challenge. However, in passively administered groups, a challenge with PCP caused a significant decline in vertical activity and a slight but significant decrease in rearing in chronically Sal-treated animals. A challenge with PCP also reduced rearing in rats chronically treated with WIN. The divergent effects of PCP on ambulation and vertical activity strengthen the hypothesis that different neuromodulatory pathways exert greater control over these two motor behaviours. In support to this, it was suggested that changes in noradrenergic activity greatly impact rearing, while locomotion is more sensitive to changes in dopaminergic activity (Miyamoto et al. 1984; Masuo et al. 1995).

Altered emotional state is also a characteristic feature of schizophrenia as patients are often diagnosed with anxiety disorders (Tibbo et al. 2003; Braga et al. 2004; Townsend and Wilson 2005; Marco et al. 2011). Thus, along with ambulation (distance travelled) and rearing (vertical activity), we also measured the time spent at the periphery of the experimental activity chamber as a measure of general anxiety-like behaviour (Gray 1979; Gentsch et al. 1987; Jinks and McGregor 1997; Cannizzaro et al. 2001), a phenomenon better known as "thigmotaxis". Thigmotaxis refers to an animal's propensity to

move along the edge of the environment, thus exploring the peripheral zone of the experimental cage. This tendency to remain close to the walls is frequently attributed to anxiety-like behaviour and is considered a phylogenetically adaptive response (Grossen and Kelley 1972; Choleris et al. 2001; Kavaliers and Choleris 2001). The validity of thigmotaxis as an indicator of anxiety-like behaviour is demonstrated via its reduction by anxiolytic agents (Treit and Fundytus 1989). Aligned with the anxiolytic effect of chronic low doses of cannabinoids (Jiang et al. 2005; Lafenêtre et al. 2007; Long et al. 2009; Hill and Gorzalka 2009; Parolaro et al. 2010), WIN-SA animals constantly showed lower thigmotaxis activity than Veh-SA animals, a behaviour that persisted even following acute and chronic PCP administration, indicating that cannabinoid self-administration reduced the anxiety induced by a PCP challenge. The mechanisms mediating the effects of cannabinoids on anxiety-related responses appear to involve the CB1 receptors. Limbic brain regions, such as the amygdala, hippocampus and cortex, contain high densities of these receptors (Katona et al. 2001; Hájos and Freund 2002; Tzavara et al. 2003; Pistis et al. 2004; Viveros et al. 2007) which regulate anxiety-related responses by modulating mainly GABAergic, serotoninergic and noradrenergic neurotransmissions (Viveros et al. 2005).

Collectively, these results revealed an attenuating effect of cannabinoid self-administration on subsequent PCP-induced motor responses, implying that cannabinoids could partially ameliorate schizotypic positive symptoms in animals. Yet, we did not find significant correlations between the level of cannabinoid intake and intensity of PCP-induced behaviours. Our data are consistent with a recent preclinical study by Long et al. (2009), showing that both THC and cannabidiol attenuate hyperlocomotion are induced by the psychostimulant dexamphetamine (see also Moreira and Guimanares 2005). Accordingly, CB1 receptor gene disruption in mice exacerbates the effects of PCP on stereotypy (Haller et al. 2005) and decreases the locomotor-activating and sensitising effects of amphetamine (Corbillé et al. 2007; Thiemann et al. 2008). Clinical evidence also support a protective role of cannabinoids against schizophrenic symptoms (Schwarcz et al. 2009; 2010), strengthening the hypothesis that schizophrenic patients may attempt to alleviate the symptoms by smoking cannabis (Arseneault et al. 2004; Bersani et al. 2002; Degenhardt et al. 2001; Peralta and Cuesta 1992; Schofield et al. 2006).

Conclusion

Locomotor and emotional parameters evaluated in the present study revealed an attenuating effect of cannabinoids on the psychotomimetic effects of PCP in adult animals. WIN-SA rats titrated their daily drug intake to maintain a subjective level of cannabinoid reward, as human addicts normally do. Notably, by examining the effect of chronic WIN treatment in animals that received the CB1 agonist on a not-voluntarily basis, we confirmed an attenuating effect of cannabinoid administration on PCP-induced schizophrenia-like positive symptoms. However, further studies are certainly needed to provide convergent validation of this hypothesis.

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Conflict of interest None.

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