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The effect of SR 141716 and apomorphine on sensorimotor gating in Swiss mice

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Abstract

The aim of the present study was to investigate in Swiss mice the acute effects of the CB_1 receptor antagonist *N*-piperidino-5-(4-chlorphenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide (SR 141716) alone and in combination with apomorphine, a D_1/D_2 receptor agonist, on prepulse inhibition (PPI) of the acoustic startle response, an operational measure of sensorimotor gating. SR 141716 (1 and 3 mg/kg ip) had no significant effect on PPI. Apomorphine (3 mg/kg ip) significantly disrupted PPI. The PPI of mice injected with SR 141716 (1 mg/kg ip) plus apomorphine (3 mg/kg ip) was not significantly different to that of vehicle plus apomorphine (3 mg/kg ip)-treated mice. However, the higher dose of SR 141716 used (3 mg/kg ip) significantly inhibited the disruption of PPI produced by apomorphine. These results suggest that antagonism of CB_1 receptors with SR 141716 has no significant effect on sensorimotor gating in Swiss mice. However, CB_1 receptors appear to be important in the effect of apomorphine on sensorimotor gating, as antagonism of CB_1 receptors with SR 141716 inhibits apomorphine-induced disruptions.

Keywords: SR 141716; Apomorphine; Startle response; Sensorimotor gating; Prepulse inhibition

1. Introduction

The primary targets of a group of compounds collectively referred to as cannabinoids, which include some components of the plant *Cannabis sativa*, are two G-protein-coupled receptors. CB_1 receptors are located primarily in the central nervous system (Devane et al., 1988) while CB_2 receptors are located in the periphery and are largely confined to the immune system (Munro et al., 1993). Radiographic binding studies have shown the highest density of CB_1 receptors to lie in the basal ganglia, the hippocampal dentate gyrus, the cerebellum and the cerebral cortex (Herkenham et al., 1990), regions which have also been associated with the pathophysiology of schizophrenia (Gray, 1995).

The isolation of the endogenous cannabinoid anandamide (Devane et al., 1992) has led to numerous investigations on the endocannabinoid system, the role of which is still far from being elucidated. Several lines of evidence suggest that the endocannabinoid system has a role in the normal functioning of brain regions associated with the pathophysiology of schizophrenia. Firstly, the hippocampus contains the highest concentration of the endogenous cannabinoid (endocannabinoid) anandamide in the human and rat brain (Felder et al., 1996). Moreover, elevated levels of anandamide were detected in the cerebrospinal fluid of schizophrenic patients (Leweke et al., 1999). Indeed, a cannabinoid hypothesis of schizophrenia that described cognitive dysfunction associated with dysregulation of an endogenous cannabinoid system has been proposed (Emrich et al., 1997).

N-piperidino-5-(4-chlorphenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide (SR 141716) has been characterised as a selective CB_1 receptor antagonist (Rinaldi-Carmona et al., 1994). SR 141716 has been reported to produce significant changes in a variety of behavioural systems in rodents, such as alterations in sleep–waking cycle (Santucci et al., 1996), incentive learning (Chaperon and Thiebot, 1999) and memory extinction (Marsicano et al., 2002). In addition, the results from several studies have suggested that it has possible antipsychotic potential. For example, SR 141716 increases fos immunoreactivity in the mesocorticolimbic system in a similar

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manner to antipsychotics (Alonso et al., 1999). Also, it has been shown that SR 141716 antagonises amphetamine-induced exploratory behaviour in gerbils, a paradigm used to test antipsychotic-like pharmacological activity (Poncelet et al., 1999).

Sensorimotor gating is the process by which an individual screens or filters the large flow of information from its surroundings (Hoffman and Ison, 1980; Ison and Hoffman, 1983). An abnormality of the sensorimotor gating pathway produces sensory overstimulation and accompanying cognitive fragmentation, or the inability to attain information from the environment and process it accordingly. This abnormality of sensorimotor gating is thought to underlie various psychotic symptoms observed in neuropsychiatric disorders, such as schizophrenia (Braff et al., 1992), obsessive compulsive disorder (Swerdlow et al., 1993), Tourette's syndrome (Castellanos et al., 1996) and Huntington disease (Swerdlow et al., 1995).

Prepulse inhibition (PPI) is the reduction in magnitude of the startle response when a weak acoustic pulse (prepulse) is presented 30–500 ms before a startling acoustic stimulus (pulse). PPI is a normal cross-species phenomenon and is thought to provide an operational measure of sensorimotor gating (Braff et al., 1992; Hoffman and Ison, 1980; Ison and Hoffman, 1983). PPI involves the activation of centrally mediated behavioural gating processes that are regulated by forebrain neural circuitry (Swerdlow, 2000a). A disruption of PPI as observed in psychotic patients is due to an abnormality in sensorimotor gating. This is observed both in nonmedicated schizotypal patients (Cadenhead et al., 1993) and in medicated but still ill schizophrenia patients (Bolino et al., 1994).

Disruption of PPI has also been shown in animal studies using drugs known to produce psychosis in humans, such as phencyclidine (PCP) and amphetamine (Geyer et al., 2001). Most experiments investigating the effect of drugs on PPI tend to use rats of varying strains. However, mice also demonstrate robust and reliable PPI which can be disrupted by agents that disrupt PPI in rats, such as apomorphine and PCP (Dulawa and Geyer, 1996). Although experimentally induced PPI deficits in rats or mice may not represent an animal model of schizophrenia per se, they do provide a valid model of sensorimotor gating deficits seen in schizophrenia (Geyer et al., 2001).

A number of studies have investigated the effect of SR 141716 on sensorimotor gating in rats. SR 141716 had no effect on PPI, but was able to block disruptions in PPI produced by the synthetic cannabinoid CB_1 receptor agonist CP 55,940 (Mansbach et al., 1996). Similar results emerged in the work of Martin et al. (2003) who also found that SR 141716 inhibited CP 55,940-mediated decreases in PPI and startle response in rats but did not reverse disruptions caused by apomorphine, amphetamine or the noncompetitive NMDA receptor antagonist MK-801. The authors concluded that restoration of PPI by antagonism of the CB_1 receptor is specific to cases of disrupted sensorimotor gating directly associated with excessive activation of CB_1 receptors (Martin et al., 2003).

The aim of the present study was to determine the effect of the CB_1 receptor antagonist SR 141716 on sensorimotor gating as measured by the effect on PPI in Swiss mice. The effect of SR 141716 was investigated in vehicle-treated mice and in mice injected with the D_1/D_2 receptor agonist apomorphine, a drug known to produce robust disruptions in sensorimotor gating.

2. Materials and methods

2.1. Animals

Male Swiss mice weighing between 20 and 25 g were used. Prior to experiments, the animals were housed in groups of six and kept at 22 °C with a 12-h light–dark cycle. Food and drinking water were available ad libitum. All mice used in the study were drug naïve. The experimental protocol was approved by the Victorian College of Pharmacy, Monash University Animal Experimentation Ethics Committee and conforms to the guidelines set out by the National Health and Medical Research Council and Australian government regulations.

2.2. Apparatus

Startle reactivity was measured using an SR-LAB startle chamber (San Diego Instruments, San Diego, CA). The animal enclosure consisted of a Perspex cylinder 40 mm in diameter on a platform, connected to a piezoelectric accelerometer which detects movement within the cylinder. Above the cylinder was a loudspeaker attached to programmable audio controls. The animal enclosure was located in an illuminated, ventilated and sound-attenuated startle chamber.

2.3. Drugs

The following drugs and solutions were used: L-apomorphine HCl (Aldrich), SR 141716 (Sanofi Recherche) and Intralipid (Baxter). SR 141716 was incorporated into the triglyceride/phospholipid emulsion vehicle Intralipid 10% v/v as described previously (Malone and Taylor, 1998). The emulsion was made up to the required volume with Intralipid so that a volume of 10 ml/kg body weight was injected in each mouse. Apomorphine was dissolved in a solution of 0.1% w/v ascorbic acid in distilled water to prevent oxidation.

2.4. Experimental procedure

All testing took place during the light phase. Animals were acclimatised in the startle chambers over three 0.5-h sessions; two sessions on the day before testing and one

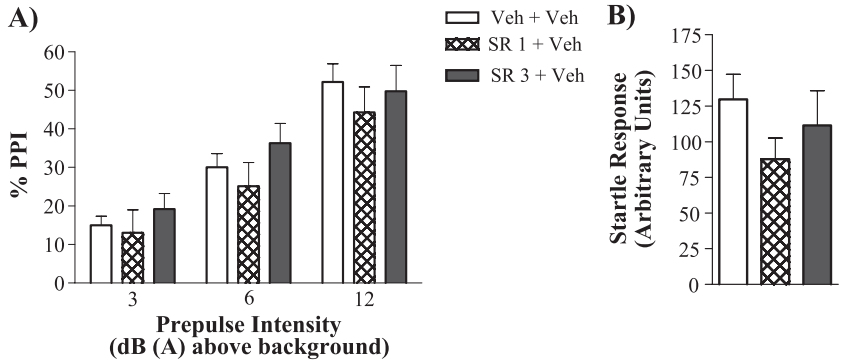

Fig. 1. (A) PPI of the startle response and (B) acoustic startle response in mice treated with SR 141716 (0–3 mg/kg ip) plus vehicle. Results are expressed as mean + S.E.M. [$n = 6–7$, $F(2,16) = 1.233$, $P = .320$ (acoustic startle response); $F(2,16) = 0.113$ $P = .894$ (PPI)].

on the morning of testing. In the afternoon of the same day, mice were administered with the test drug(s) and were then placed in their home cage for an interval which varied according to the drug used (see below). Animals were then placed in the startle chamber enclosure. After 5-min acclimatisation to the background noise of 70 dB(A), startle stimuli of 120-dB intensity and 40-ms duration were applied, either alone or preceded by 100 ms with a prepulse of 20-ms duration and intensity 3–12 dB above background. Prepulse-alone trials of 3, 6 and 12 dB(A) above background were also presented, as were trials containing no stimulus at all (background). Ten trials of each type were presented in a pseudorandom order with an average interval of 15 s separating each trial (each trial interval ranged from 8 to 22 s). An extra 10 pulse-alone trials were presented at the beginning and end of each test session, but were not used in the calculation of PPI values. The whole body flinch (movement) elicited by the presentation of each trial type was detected by the accelerometer, and the PPI calculated as a percentage of this startle response using the formula % PPI=[1-(startle amplitude after prepulse–pulse pair/startle amplitude after pulse only)] × 100. A 0% value indicates that there is no difference between the startle responses (movement) to pulse + prepulse trials and pulse-alone trials. Positive values indicate the extent to which the startle response is diminished in the presence of a prepulse.

Mice were administered with either vehicle control for SR 141716 (Intralipid) plus vehicle control for apomorphine (0.1 % ascorbic acid in distilled water), SR 141716 (1 or 3 mg/kg ip) plus vehicle control (Fig. 1), vehicle control plus apomorphine (0.3, 1 or 3 mg/kg ip; Fig. 2), SR 141716 (1 or 3 mg/kg ip) plus apomorphine (1 mg/kg ip; data not shown) or SR 141716 (1 or 3 mg/kg ip) plus apomorphine (3 mg/kg ip; Fig. 3). When used, SR 141716 and apomorphine were administered 45 min and 15 min, respectively, before mice were placed in the startle chamber for testing.

2.5. Statistics

A one-way ANOVA was used to compare startle responses to the 120-dB(A) pulse alone between treatment groups. A two-way repeated-measures ANOVA was used to compare PPI values between treatment groups. When a main effect of treatment on startle response or PPI was found to be significant ($P < .05$) a Dunnett's multiple comparison versus control (vehicle) post hoc test was used

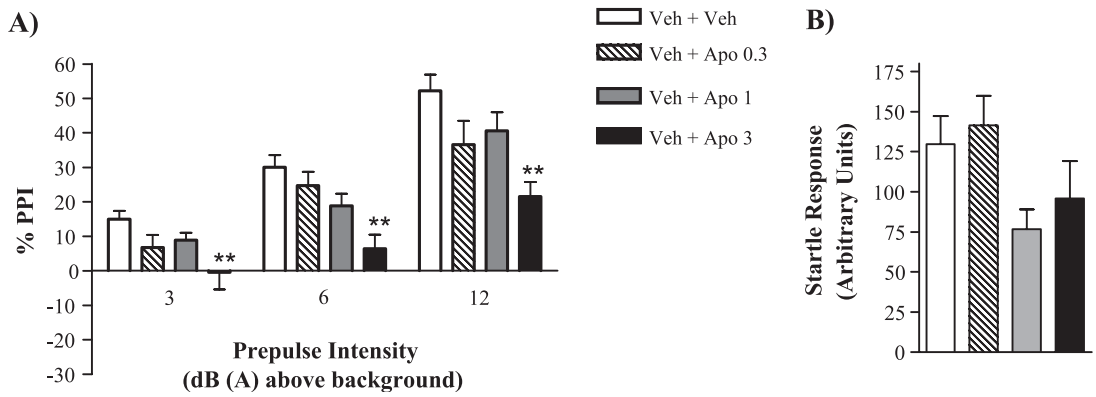

Fig. 2. (A) PPI of the startle response and (B) acoustic startle response in mice treated with vehicle plus apomorphine intraperitoneally. Results are expressed as mean + S.E.M. [$n = 6–12$, $F(3,20) = 2.787$, $P = .067$ (acoustic startle response); $F(3,20) = 7.054$, $P = .002$ (PPI; $^{**}P < .01$ vs. vehicle-treated group [Dunnett's test])].

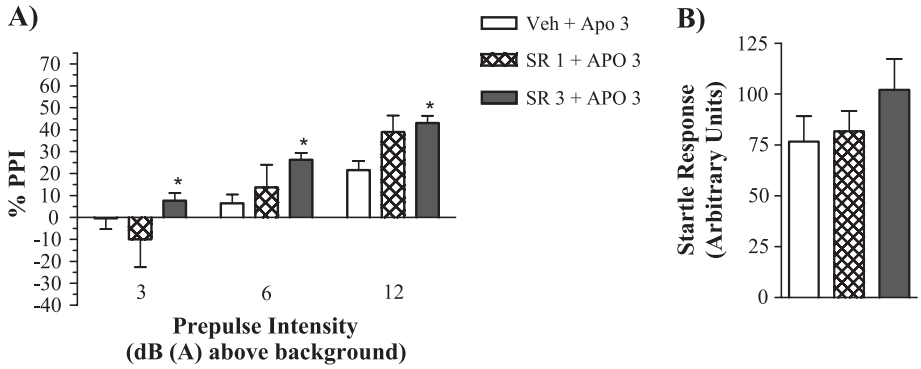

Fig. 3. (A) PPI of the startle response and (B) acoustic startle response in mice treated with SR 141716 1 and 3 mg/kg 30 min before treatment with apomorphine 3 mg/kg. Results are expressed as mean + S.E.M. [$n = 6–11$, $F(2,20) = 0.932$ (acoustic startle response); $F(2,20) = 3.862$, $P = .038$ (PPI; $^*P < .05$ vs. vehicle + apomorphine-treated group [Dunnett's test])].

to determine the level of significance for each treatment group. The main effect of prepulse intensity on PPI was also obtained from this analysis. Statistical analyses were performed with SPSS 11.5 for Windows (SPSS; Chicago, USA).

3. Results

3.1. Startle response

There was no significant effect of SR 141716 (plus vehicle) on the mean startle response compared to vehicle controls [$F(2,16) = 1.233$, $P = .320$; Fig. 1B; $n = 6–7$]. Apomorphine (plus vehicle) had no significant effect on the mean startle response [$F(3,20) = 2.787$, $P = .067$; Fig. 2B; $n = 6–12$].

SR 141716 (1 or 3 mg/kg) administered 30 min before apomorphine (1 mg/kg) had no significant effect on startle response compared with that of vehicle- and apomorphine-treated mice [$F(2,12) = 1.731$, $P = .219$; data not shown; $n = 6$]. There was no significant difference in mean startle response of SR 141716 (1 or 3 mg/kg) administered 30 min before apomorphine (3 mg/kg), compared with that of vehicle- and apomorphine-treated mice [3 mg/kg; $F(2,20) = 0.932$, $P = .410$; Fig. 3B; $n = 6–11$].

3.2. Prepulse inhibition

There was a main effect of prepulse level on PPI in all experiments ($P < .001$), with greater prepulse level producing a greater PPI. There was no significant interaction between prepulse intensity and drug condition between any experiments (data not shown).

SR 141716 (1 or 3 mg/kg) and vehicle had no significant effect on PPI when compared with vehicle controls [$F(2,16) = 0.113$, $P = .894$; Fig. 1A].

There was a significant effect of apomorphine (plus vehicle) treatment on PPI [$F(3,20) = 7.054$, $P = .002$; Fig. 2A]. Post hoc comparisons indicated that the disruption of PPI by apomorphine (plus vehicle) was significant for the 3-mg/kg apomorphine dose ($P = .001$) when compared with vehicle controls.

There was no significant effect on PPI of SR 141716 (1 or 3 mg/kg) plus apomorphine 1 mg/kg compared with vehicle plus apomorphine 1 mg/kg [$F(2,12) = 1.503$, $P = .261$; data not shown].

SR 141716 administered before apomorphine (3 mg/kg) significantly reversed the disruption in PPI elicited in mice given vehicle plus apomorphine (3 mg/kg) [$F(2,20) = 3.862$, $P = .038$; Fig. 3A]. Post hoc comparisons indicated that the disruption of PPI by apomorphine (plus vehicle) was reversed by the 3-mg/kg dose of SR 141716 ($P = .030$).

4. Discussion

In all experiments, the level of PPI, or the degree of inhibition of the startle reflex by the prepulse, increased proportionally to the prepulse level. This is in agreement with previous studies in rodents (Dulawa and Geyer, 1996; Swerdlow et al., 2000b) and validates PPI as an operational measure of sensorimotor gating. Mice treated with the respective vehicle controls for SR 141716 (Intralipid) and apomorphine (0.1% ascorbic acid in distilled water) displayed similar PPI to that observed in our laboratory previously (unpublished observations) and to that in a report that used the same prepulse intensities as in the present study in mice (Dulawa and Geyer, 1996), indicating that the vehicles used in the present study do not significantly alter PPI.

The disruption of PPI induced by apomorphine is consistent with previous studies which have shown that apomorphine produces significant disruption of PPI in mice (Curzon and Decker, 1998; Dulawa and Geyer, 1996; Ralph-Williams et al., 2003; Varty et al., 2001). The most frequently used model of disrupted PPI in rodents is the dopaminergic model in which dopamine agonists, such as apomorphine, are used to disrupt PPI (Geyer et al., 2001). The higher doses of apomorphine (3 mg/kg) required to

elicit disruptions in PPI in mice are consistent with previous studies in which comparably higher apomorphine doses were required to disrupt PPI in mice than in rats (Curzon and Decker, 1998; Dulawa and Geyer, 1996; Ralph-Williams et al., 2003; Varty et al., 2001).

Apomorphine had no significant effect on the mean startle response, although there was a tendency for a decrease in startle magnitude (Fig. 2B). While previous studies have shown that apomorphine has no significant effect (Curzon and Decker, 1998) on mean startle response or an effect only at high doses (Varty et al., 2001), it has been reported that apomorphine induces a reduction in startle response in mice at doses comparable to that used in the present study (Ralph-Williams et al., 2003). Mouse strain differences may explain these varying results. A decrease in startle magnitude may imply that any disruption in PPI observed may be due to an inhibition in locomotor activity as opposed to a disruption in sensorimotor gating processes (Mansbach et al., 1996). However, in the Ralph-Williams et al. (2003) study, the investigators did not acclimatise the mice to the startle chambers as was done in the present study. The mice in the present study were acclimatised to the startle chambers over three 0.5-h sessions; two sessions on the day before testing and one on the morning of testing. It has been shown that acclimatisation produces more stable results on PPI (Faraday and Grunberg, 2000).

The CB_1 receptor antagonist SR 141716 had no effect on mean startle response or on PPI (Fig. 1). This is in agreement with a number of studies in rats using SR 141716A, the hydrochloride salt of SR 141716 (Mansbach et al., 1996; Martin et al., 2003). This indicates that sensorimotor gating in mice is unaffected by the antagonism of CB_1 receptors.

The main finding of the present study is that SR 141716 reversed apomorphine-induced disruption of PPI. This is in contrast to the report of Martin et al. (2003) who found that while SR 141716A was able to reverse CB_1 receptor-agonist-mediated decreases in PPI and startle response in male Wistar rats, SR 141716A did not reverse disruptions caused by apomorphine, amphetamine or the noncompetitive NMDA receptor antagonist MK-801. It is obviously difficult to directly compare these experiments with the current study due to the differences of species used. It has been shown that optimal conditions for disruption of PPI by apomorphine in mice may differ from those used in rats (Varty et al., 2001). It is possible that this may be due to slight but potentially significant differences occurring in the neurotransmitter pathways mediating PPI in mice compared to rats. To the best of our knowledge, this is the first study that has investigated the effect of SR 141716 on sensorimotor gating in mice.

Apart from species differences, several experimental parameters differ in the present study to that of Martin et al. (2003). Firstly, we used the fat emulsion Intralipid to incorporate SR 141716 into an injectable formulation, whereas Martin et al. (2003) used 0.5% (w/v) carboxymethylcellulose in physiological saline. The pharmacokinetics of SR 141716 may be altered depending on what vehicle is used. Secondly, in Martin et al. (2003), SR 141716A and apomorphine were injected 30 min and immediately before the rats were placed in the startle chambers, respectively, whereas in the present study, SR 141716 and apomorphine were injected 45 and 15 min before mice were placed in the startle chambers, respectively. As in the present study, SR 141716 is commonly administered 30 min before a subsequent drug injection in mice (Martellotta et al., 1998; Souilhac et al., 1995). Although this difference in time of SR 141716 administration exists, it would be expected to be acting as an antagonist throughout the sessions in both cases.

Thirdly, Martin et al. (2003) used an intertrial interval average of 7.5 s compared to the 15-s average intertrial interval used in the present study. Finally, Martin et al. (2003) exposed rats to a screening session that included 17 pulse-alone and 3 prepulse + pulse trials on the day before the experiment, whereas in the present study, mice were acclimatised twice the day before and once the morning of the experiment with background noise only. In the present study, a prescreening session was not used as previous observations in our laboratory have shown that startle response for vehicle-treated Swiss mice does not significantly alter. This was confirmed by results obtained in the present study which showed no significant difference in startle response across all treatment groups. Prehabituation to test enclosures can significantly modify behavioural results obtained. This was one possible explanation put forward by Martin et al. (2003) in accounting for the observation that SR 141716A has been shown to reverse the effects of amphetamine in gerbils (Poncelet et al., 1999), whereas Martin et al. (2003) found no reversal of effect by SR 141716A on behavioural effects produced by amphetamine. Given these differences between the methodology employed in the Martin et al. (2003) study and the present study, it is difficult to make direct comparisons with respect to the effects of SR 141716 on apomorphine-induced disruptions in PPI.

Several studies have shown that apomorphine-induced disruptions in PPI can be reversed by drug pretreatment. In the CD-1 mouse strain, pretreatment with the antipsychotic haloperidol attenuated the apomorphine-induced disruption of PPI (Curzon and Decker, 1998). Furthermore, the D_1 family receptor antagonist SCH23390 blocked the PPI-disrupting effects of apomorphine, but the D_2 family receptor antagonist raclopride failed to alter the disruptive effect of apomorphine in C57BL/6J mice (Ralph-Williams et al., 2003). Thus, it appears that apomorphine-induced disruptions in PPI in mice can be reversed by drugs that block D_1 receptors.

Although SR 141716 has been described as a potent and selective CB_1 receptor antagonist in mice (Compton et al., 1996; Rinaldi-Carmona et al., 1994), the ability of SR

141716 to attenuate apomorphine-induced disruptions of PPI in mice may be due to a number of other mechanisms. SR 141716 displays inverse agonist activity in vitro (Landsman et al., 1997; MacLennan et al., 1998; Mato et al., 2002; Meschler et al., 2000; Sim-Selley et al., 2001). While this effect of SR 141716 has not been categorically proven in vivo, a number of in vivo studies lead to the possibility that SR 141716 is either acting as an inverse agonist and/or that SR 141716 is blocking the endocannabinoid system, which may be tonically active under certain conditions. For example, SR 141716 reduces memory deficits in rats and mice (Mazzola et al., 2003; Terranova et al., 1996), produces hyperalgesia in mice (Richardson et al., 1997), decreases food intake in obese mice (Ravinet Trillou et al., 2003) and increases several behavioural effects in rats, such as scratching and grooming (Jarbe et al., 2002). In all of these studies, it is suggested that SR 141716 is producing its pharmacological effects through CB_1 receptor antagonism which in turns blocks the effect of endogenous cannabinoids. This is in agreement with the present study because an inverse agonist may be expected to have an effect on sensorimotor gating when administered alone. Thus, if SR 141716 is acting via antagonism at CB_1 receptors, it may be suggested that apomorphine-induced disruptions in PPI require an intact and functioning endocannabinoid system.

However, a recent study suggests that SR 141716A-induced stimulation of locomotor activity in mice is neither the result of blocking endocannabinoid tone via CB1 receptor antagonism nor the result of inverse agonist activity (Bass et al., 2002). These authors suggested that SR 141716A may be acting at an "unknown" central receptor as their SR 141716A analogues that had very little affinity for the CB_1 receptor could stimulate locomotor activity and the analogues that produced inverse agonism did not stimulate locomotor activity. However, the doses of SR 141716 used to produce an increase in locomotor activity were 30 mg/kg ip, which is 10 times higher than the maximum dose used in the present study. In the present study, SR 141716 inhibited apomorphine-induced disruptions in PPI at doses thought to produce selective antagonism at CB_1 receptors (Compton et al., 1996; Rinaldi-Carmona et al., 1994). Further investigation is required to confirm whether apomorphine-induced disruption of PPI is mediated via the endogenous cannabinoid system. For example, it would be interesting to investigate whether apomorphine is able to alter levels of endogenous cannabinoids in brain regions known to be associated with the sensorimotor gating pathway. Future studies are also required to determine if other neurotransmitter mechanisms are altered by SR 141716 which may result in a reversal of apomorphine-induced disruptions in sensorimotor gating.

It has also been shown, albeit in rats, that PPI deficits induced by the CB_1 receptor agonist WIN 55212-2 can be reversed by the D_1/D_2 receptor antagonist haloperidol (Schneider and Koch, 2002). It was suggested by these authors that the disruption in PPI by WIN55212-2 is due to an overactivity of the mesoaccumbal dopaminergic system. Assuming SR 141716 is acting as an antagonist at CB_1 receptors, the results of the present study suggest that blockade of the endogenous cannabinoid system can block the disrupting effects of the D_1/D_2 receptor agonist apomorphine. It would be interesting to investigate if the reverse is true, that is, whether cannabinoid agonists can disrupt PPI in mice through an overactivity of the dopaminergic system.

In conclusion, the results of the present study suggest that SR 141716 has no significant effect on startle response or PPI. However, the disruptions in PPI produced by the D_1/D_2 receptor agonist apomorphine can be blocked by SR 141716 at doses at which SR 141716 is a selective CB_1 receptor antagonist. This suggests that the endocannabinoid system may contribute to the apomorphine-induced disruption of sensorimotor gating.

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