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ORIGINAL INVESTIGATION

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Blockade of cannabinoid (CB1) receptors by SR 141716 selectively antagonizes drug-induced reinstatement of exploratory behaviour in gerbils

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Abstract *Rationale*: A cannabinoid hypothesis of schizophrenia has been proposed according to which cognitive dysfunction could be associated with dysregulation of an endogenous cannabinoid system. *Objective*: The present study investigated whether SR 141716, a selective CB1 receptor antagonist, was able to reduce the hyperactivity induced in gerbils by various stimulant drugs known to produce or exacerbate schizophrenic symptoms. *Methods*: Cocaine, *d*-amphetamine, morphine, and Win 55212-2 were administered intraperitoneally (IP) either immediately before placing the animals in the test apparatus (non-habituated gerbils) or after a 2- to 3-h habituation period in the actimeter (habituated gerbils). SR 141716 was given IP 30 min before the injection of stimulant drugs. Horizontal activity was recorded every 10 min for 1 h in Digiscan activity monitor. *Results*: SR 141716 (0.3–3 mg/kg) dose-dependently suppressed the enhanced locomotor activity induced by each stimulant drug in habituated gerbils, but not in non-habituated animals. Clozapine, an atypical antipsychotic compound, but not haloperidol, shared with SR 141716, the ability to differentially affect drug-induced hyperactivity in habituated versus non-habituated gerbils. *Conclusion*: The activation of cannabinoid systems is a required, permissive element in the ability of cocaine, *d*-amphetamine, morphine, and Win 55212-2 to reinstate behaviour, i.e., to override stimulus satiation.

Key words Cannabinoid receptor · Locomotor activity · Habituation · Antipsychotic drug · Gerbils

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Introduction

Marijuana (*Cannabis sativa*) is one of the oldest and most widely used drugs in the world. The identification and cloning of the cannabinoid CB1 and CB2 receptors (Matsuda et al. 1990; Munro et al. 1993) and the discovery of putative endogenous ligands, anandamide (Devane et al. 1992) and sn-2-arachidonylglycerol (Mechoulam et al. 1995; Stella et al. 1997) opened new avenues of cannabinoid research aimed at understanding the physiological role of this neurochemical system.

SR 141716 has been characterized as a selective CB1 versus CB2 ligand acting as an antagonist against a variety of pharmacological and behavioural cannabinoid effects in rodents (Rinaldi-Carmona et al. 1994; Shire et al. 1996). The observation that by itself this antagonist may markedly affect several behavioural or physiological parameters, including sleep-waking cycle (Santucci et al. 1996), rate of forgetting (Terranova et al. 1996), sucrose intake (Arnone et al. 1997) and incentive learning (Chaperon et al. 1998), further reinforces the possibility of spontaneously active endogenous cannabinoid systems. Although current data converge to suggest that such systems play a major role in synaptic regulation (Aceto et al. 1995; Collins et al. 1995; Terranova et al. 1995; Tsou et al. 1995), little is known about their potential involvement in pathopsychological conditions.

Recently, Emrich et al. (1997) proposed a cannabinoid hypothesis of schizophrenia according to which cognitive dysfunction could be associated with dysregulation of an endogenous cannabinoid system. This hypothesis was mainly based on the observation of high CB1 receptor density in brain structures involved in higher cognitive and emotional functions and the association between cannabis abuse and production, exacerbation or relapse of schizophrenic symptomatology.

Using SR 141716 as a tool, the present study investigated whether endogenous cannabinoid systems may operate in rodent behavioural models classically used to predict antipsychotic activity (Moore and Gershon 1989) such as enhanced locomotion elicited by drugs able to

produce or exacerbate schizophrenic symptoms (Bell 1973; Snyder 1973; Segal and Schuckit 1983). The drugs chosen to produce hyperactivity were cocaine, *d*-amphetamine, morphine, and a cannabinoid receptor agonist, Win 55212-2, each drug being given either when the animals were placed in the test apparatus or after a 2- to 3-h period of habituation.

The present investigations were performed with Mongolian gerbils because locomotion in this species is reportedly less dependent upon fear-related reactions than in rats or mice, and thus may represent a more valuable index of information processing and stimulus satiation, i.e. of exploration (Thompson and Lippman 1972; Osborne 1977; Cheal 1983).

Materials and methods

Animals

Adult male Mongolian gerbils (*Meriones unguiculatus*) weighing 60–80 g, (CERJ, France) were used. One week before experiments, gerbils were caged in groups of six, in a room at constant temperature (21±1°C) on an automatic dark/light schedule (light 7 a.m. to 7 p.m.) with food and water freely available. All procedures were approved by the Comité d'Expérimentation Animale of Sanofi Recherche (Animal Care and Use Committee of Sanofi Recherche) and were carried out in accordance with French legislation (décret no. 87-848, 19 Octobre 1987; and arrêté, 19 Avril 1988) which implemented the European directive 86/609/EEC.

Drugs

SR 141716 [*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide] (Sanofi Recherche, Montpellier, France), Win 55212-2 mesylate (RBI) and clozapine (Sandoz) were suspended with 0.01% Tween 80 in distilled water. Cocaine chlorhydrate, *d*-amphetamine sulphate, (Coopérative pharmaceutique française), and morphine chlorhydrate (Francopia), were dissolved in distilled water. Haloperidol chlorhydrate (Sigma) was dissolved in tartaric acid (0.1%) and distilled water. The injection volume for the IP route was 0.5 ml/100 g body weight.

Apparatus

Horizontal activity was measured for gerbils individually placed in a Digiscan animal activity monitor (Omnitech Electronics, Columbus, Ohio, USA). Each monitor consisted of a 42×42×30.5 cm clear Plexiglas box with a grid of 16 infrared beams 2.5 cm apart from front to back and from side to side. Monitors were connected to a Digiscan Analyzer that transmitted the activity data to a microcomputer.

Procedure

SR141716 (0.3–1–3–10 mg/kg IP) was administered 30 min before IP administration of cocaine, *d*-amphetamine, morphine, and Win 55212-2 in non-habituated and habituated gerbils. Non-habituated gerbils were administered cocaine, *d*-amphetamine, morphine or Win 55212-2 and immediately placed in the Digiscan cage. Habituation consisted of a 2- to 3-h drug-free period (necessary period to extinguish spontaneous locomotor activity) before cocaine, *d*-amphetamine, morphine, and Win 55212-2 administration. Locomotor activity (number of beams interruptions on the horizontal sensors) was measured every 10 min for 1 h, beginning immediately after the stimulant drug administration. Groups of 8–25 animals were used.

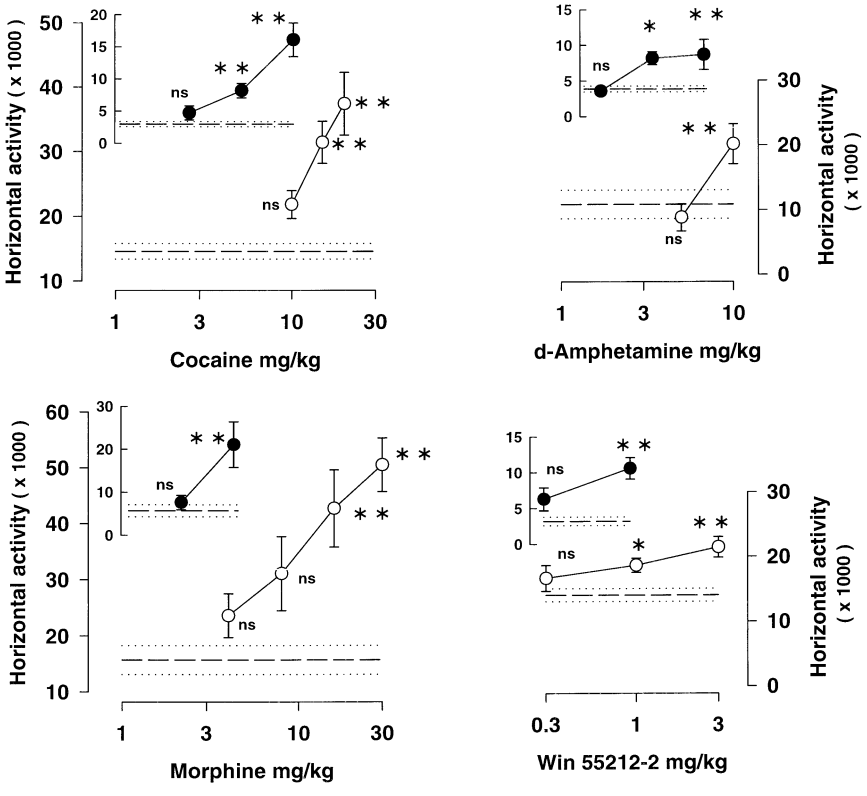

Fig. 1 Dose-effect relationship of cocaine, *d*-amphetamine, morphine and Win 55212-2 on locomotor activity (mean±SEM). Locomotor activity was measured during a 60-min test period. Non-habituated gerbils (○) were placed in the test apparatus immediately after being administered (IP) with stimulant drugs. Habituated gerbils (●) were given (IP) stimulant drugs after a 2- to 3-h drug-free period in the actimeter. ÷÷÷÷ Represents vehicle control level (mean±SEM). **P*≤0.05; ***P*≤0.01; *ns*, non-significant versus vehicle control group (Dunnett's *t*-test)

Statistical analyses were performed using ANOVA followed by Dunnett's *t*-test. Calculation of ID_{50} values with 95% fiducial limits were calculated using a Probit method. Linear regressions for the antagonistic effect of SR 141716 against each stimulant drug were calculated using ANOVA.

Results

Drug-induced hyperactivity in non-habituated and habituated gerbils

Figure 1 shows that cocaine, *d*-amphetamine, morphine, and Win 55212-2 dose-dependently increased horizontal activity. The first doses producing a significant increase in locomotor activity were: in non-habituated gerbils 15, 10, 16 and 3 mg/kg and in habituated gerbils 5, 2.5, 4 and 1 mg/kg for cocaine, *d*-amphetamine, morphine and Win 55212-2, respectively.

Effect of SR 141716

Figure 2A shows that SR 141716 (0.3–3 mg/kg) significantly and dose-dependently antagonized cocaine (5 mg/kg)-induced hyperactivity in habituated gerbils [linear regression, $F(1,72)=14.74$; $P\leq0.001$] with an ID_{50} of 0.38

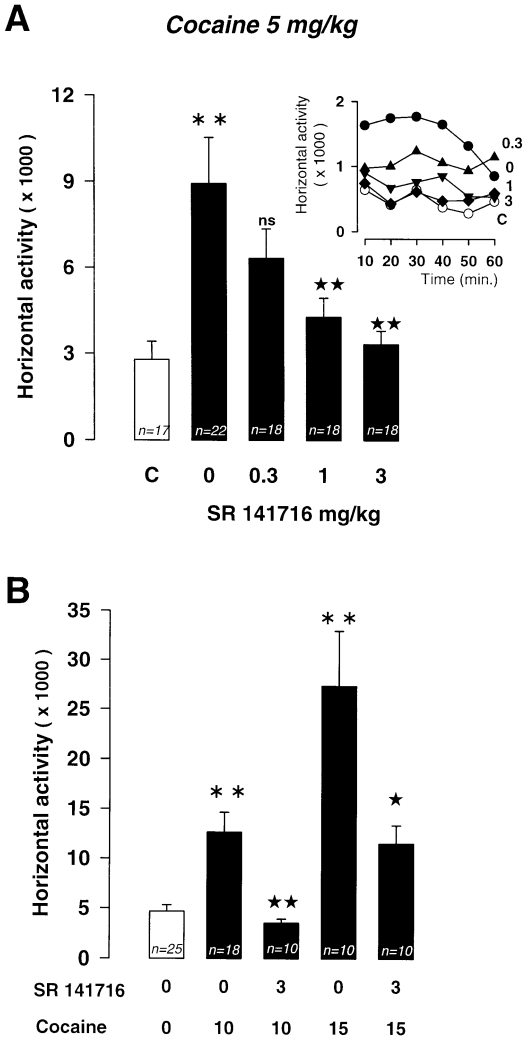

Fig. 2A, B Effect of SR 141716 (IP) on cocaine (5 mg/kg IP)-induced hyperactivity (**A**) and cocaine (10 and 15 mg/kg IP)-induced hyperactivity (**B**) in habituated gerbils evaluated during 60 min. *Insert* (**A**) represents the time-course of the reinstatement of locomotor activity by 10 min fractions during 1 h. *n*=number of gerbils. ***P*≤0.01 versus vehicle control group (*C*), ★*P*≤0.05; ★★*P*≤0.01, *ns*, non-significant versus cocaine alone group. (Dunnett's *t*-test)

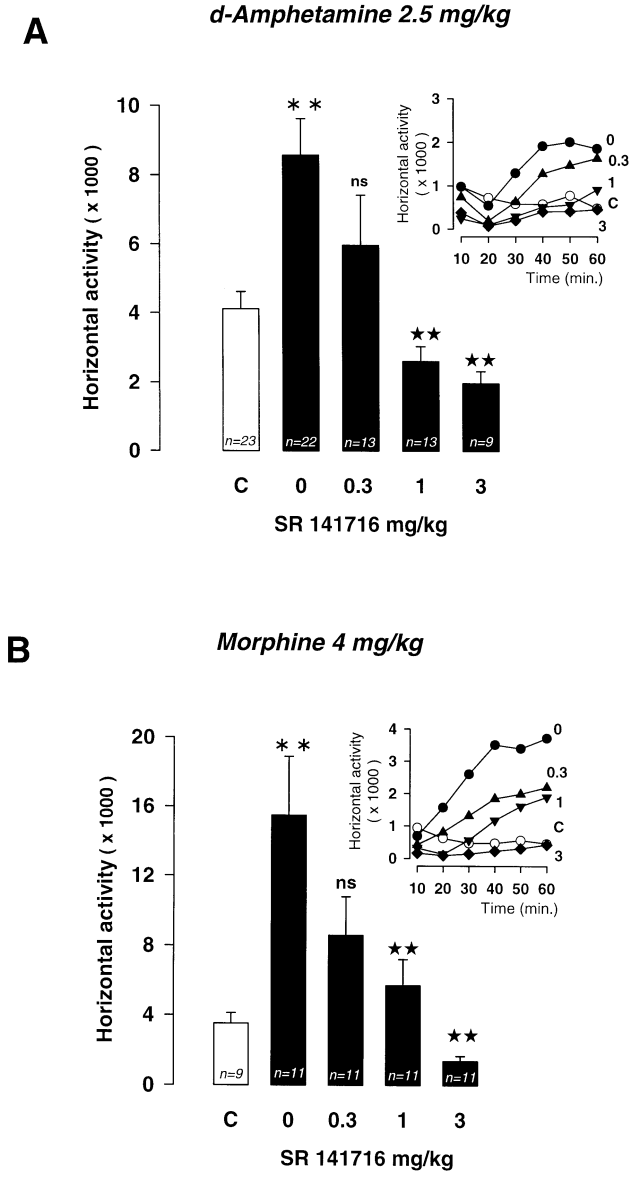

Fig. 3A, B Effect of SR 141716 (IP) on *d*-amphetamine (2.5 mg/kg IP)-induced hyperactivity (**A**) and on morphine (4 mg/kg IP)-induced hyperactivity (B) in habituated gerbils evaluated during 60 min. *Insert* (**A** and **B**) represents the time-course of the reinstatement of locomotor activity by 10-min fractions during 1 h. *n*=number of gerbils. ***P*≤0.01 versus vehicle control group (*C*), ★★*P*≤0.01, *ns*, non-significant versus *d*-amphetamine alone or morphine alone group. (Dunnett's *t*-test)

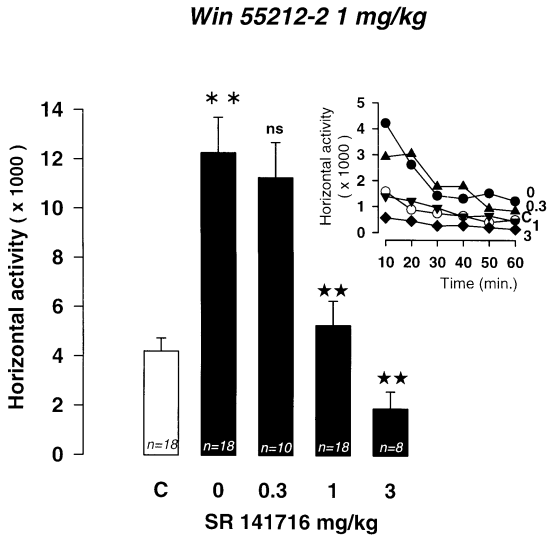

Fig. 4 Effect of SR 141716 (IP) on Win 55212-2 (1 mg/kg IP)-induced hyperactivity in habituated gerbils evaluated during 60 min. *Insert* represents the time-course of the reinstatement of locomotor activity by 10-min fractions during 1 h. *n*=number of gerbils. ***P*≤0.01 versus vehicle control group (*C*), ★★*P*≤0.01, *ns*, non-significant versus Win 55212-2 alone group. (Dunnett's *t*–test)

mg/kg (0.26–0.49, 95% fiducial limits). Doses of cocaine higher than 5 mg/kg, such as 10 and 15 mg/kg, induced strong hyperactivities that were also significantly antagonized by 3 mg/kg SR 141716 (Fig. 2B). In non-habituated gerbils, SR 141716 (0.3–3 mg/kg IP) did not antagonize cocaine (15 mg/kg)-induced hyperactivity (see Table 1).

Figures 3 and 4 show that SR 141716 (0.3–3 mg/kg) significantly and dose-dependently antagonized *d*-amphetamine (2.5 mg/kg)-, morphine (4 mg/kg)- and Win 55212-2 (1 mg/kg)-induced hyperactivity in habituated gerbils with linear regressions of $F(1,53)=20.24$, $P\leq0.001$; $F(1,50)=33.69$, $P\leq0.001$; and $F(1,40)=21.90$, $P\leq0.001$, respectively, and ID_{50}s of 0.39 mg/kg (0.003–1.7, 95% fiducial limits), 0.28 mg/kg (0.23–0.33, 95% fiducial limits) and 0.55 mg/kg (0.49–0.62, 95% fiducial limits), respectively.

In contrast, in non-habituated gerbils, SR 141716 did not antagonize *d*-amphetamine (10 mg/kg)- or morphine (16 mg/kg)-induced hyperactivity (Table 1). Win 55212-2 (3 mg/kg)-induced hyperactivity was significantly antagonized by only 10 mg/kg SR 141716 (see Table 1).

SR 141716 (3–10 mg/kg) did not significantly modify spontaneous locomotor activity in non-habituated animals (controls=9298±852; SR 3 mg/kg=8257±1439; SR 10 mg/kg=8195±906) or habituated gerbils (controls=3549±395; SR 3 mg/kg=3670±677; SR 10 mg/kg=4029±1115).

The antagonism exerted by SR 141716 appeared to be independent of the time-course effect of stimulant drugs. The effects of SR 141716 were as marked when hyperactivity was rapid in onset and stable (*d*-amphetamine and cocaine) or rapidly declining (Win 55212-2) or when hyperactivity was slow in onset and progressively increasing (morphine). Rough observations of the animals showed that reinstatement of locomotion after stimulant drugs in habituated gerbils corresponded with a pattern of locomotor activity indistinguishable from that produced by these same drugs in non-habituated animals.

Effect of antipsychotic drugs

Figure 5A shows that clozapine at a dose (3 mg/kg IP) producing no significant effect on spontaneous locomotor activity (controls=3551±333; clozapine 3 mg/kg=

Table 1 Effect of SR 141716 on cocaine (15 mg/kg)-, *d*-amphetamine (10 mg/kg)-, morphine (16 mg/kg)- and Win 55212-2 (3 mg/kg)-induced hyperactivity in non-habituated gerbils evaluated during 60 min. *n*=number of gerbils. **P*≤0.05; ***P*≤0.01 versus vehicle control group, ★★*P*<0.01; *ns*, non-significant versus Win 55212-2 alone group (Dunnett's *t*-test)

SR 141716 (mg/kg IP)	Stimulant drugs (mg/kg IP)	Horizontal activity (mean±SEM)	*n*
0	Cocaine 0	12548±1377	8
0	15	25473±2721**	14
0.3	15	32259±4237 ns	12
1	15	30949±3746 ns	13
3	15	31320±3220 ns	13
0	*d*-Amphetamine 0	7115±1497	12
0	10	12535±1567*	12
0.3	10	12851±2076 ns	12
1	10	11216±1262 ns	12
3	10	10145±1347 ns	12
10	10	13251±2011 ns	12
0	Morphine 0	16545±1349	14
0	16	41803±4701**	14
0.3	16	40012±4970 ns	14
1	16	36723±6737 ns	14
3	16	32532±7509 ns	14
10	16	41497±5017 ns	14
0	Win 55212-2 0	11220±697	12
0	3	15917±1651*	12
3	3	12097±1814 ns	12
10	3	9117±923★★	12

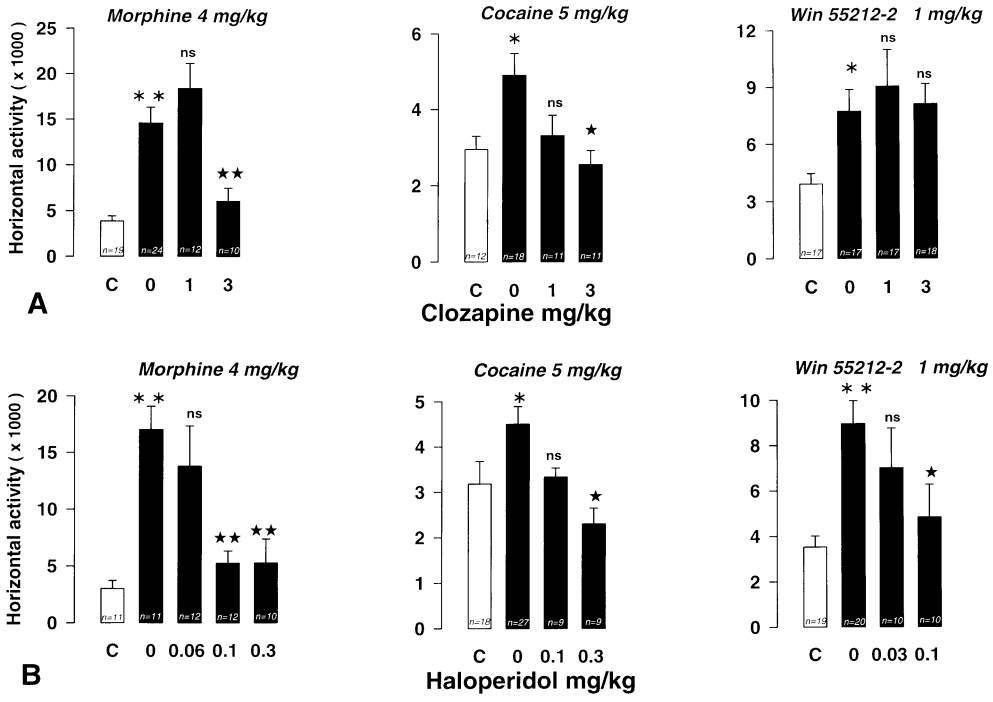

Fig. 5A, B Effect of clozapine (**A**) and haloperidol (**B**) on morphine (4 mg/kg)-, cocaine (5 mg/kg)- and Win 55212-2 (1 mg/kg)-induced hyperactivity in habituated gerbils evaluated during 60 min. *n*=number of gerbils. **P*≤0.05; ***P*≤0.01 versus vehicle control group (*C*), ⋆*P*≤0.05; ⋆⋆*P*≤0.01, *ns*, non-significant versus morphine alone, cocaine alone or Win 55212-2 alone group. (Dunnett's *t*-test)

Table 2 Effect of clozapine and haloperidol on cocaine (15 mg/kg)- and morphine (16 mg/kg)-induced hyperactivity in non-habituated gerbils evaluated during 60 min. *n*=number of gerbils. **P*≤0.05; ***P*≤0.01 versus vehicle control group, ⋆*P*≤0.05; ⋆⋆*P*≤0.01; *ns*, non-significant versus cocaine alone or morphine alone group (Dunnett's *t*-test)

Compounds (mg/kg IP)	Stimulant drugs (mg/kg IP)	Horizontal activity (mean±SEM)	*n*
Clozapine 0	Cocaine 0	12822±934	14
0	15	19612±2207*	20
3	15	27073±5722 ns	12
0	Morphine 0	15534±3055	9
0	16	44257±5896**	9
3	16	50521±6402 ns	9
Haloperidol 0	Cocaine 0	10490±1265	9
0	15	23683±3696*	13
0.1	15	19747±3199 ns	11
0.3	15	12536±3168⋆	8
0	Morphine 0	11065±1271	12
0	16	45816±5517**	12
0.1	16	31483±4636 ns	12
0.3	16	20159±3942⋆⋆	12

3210±349, ns) suppressed morphine (4 mg/kg)- and cocaine (5 mg/kg)- but not Win 55212-2 (1 mg/kg)-induced hyperactivity in habituated gerbils. In contrast, clozapine (3 mg/kg) did not counteract morphine (16 mg/kg)- or cocaine (15 mg/kg)-induced hyperactivity in non-habituated gerbils (Table 2). Haloperidol (0.1 or 0.3 mg/kg) significantly antagonized morphine- cocaine- and Win 55212-2-induced hyperactivity in habituated (Fig. 5B) and non-habituated gerbils (Table 2). At these doses however, haloperidol produced deleterious effects on spontaneous locomotor activity (controls=3281±258; halo. 0.03 mg/kg=3000±624, ns; halo. 0.06 mg/kg= 2079±379, *P*≤0.05; halo. 0.1 mg/kg=1832±264, *P*≤0.01 and halo. 0.3 mg/kg=1430±270 *P*≤0.01 in habituated gerbils and controls=15007±1549; halo. 0.1 mg/kg= 8593±1412, *P*≤0.05; halo 0.3 mg/kg=8157±1614, *P*≤ 0.05 in non-habituated gerbils).

Discussion

The main finding of the present study is that blockade of CB1 receptors exerts a differential effect on drug-induced hyperactivity depending on whether the animals were habituated or not to the test situation.

SR 141716, a selective cannabinoid CB1 receptor antagonist dose-dependently suppressed the stimulation of locomotor activity produced by *d*-amphetamine, cocaine, morphine in habituated gerbils. Remarkably, SR 141716 was found to suppress drug-induced locomotion even when the absolute level of performance of the animals was very high.

Conversely, hyperlocomotion produced by these same drugs in naive animals was impervious to CB1 receptor blockade. Indeed, SR 141716, even at doses able to abolish drug-induced hyperactivity in habituated animals,

was almost totally ineffective in reducing the ability of morphine, *d*-amphetamine or cocaine to enhance locomotion in naive gerbils. This is unlikely to be simply due to the higher dose of drug used to enhance locomotion in non-habituated versus habituated animals. Indeed, in a control experiment, performed using cocaine at the high dose of 15 mg/kg to enhance locomotion in habituated gerbils, we found that SR 141716 retained its antagonistic activity.

In the range of doses tested, SR 141716 was found not to affect spontaneous locomotor activity, whether the animals were habituated or not to the test situation. It is thus unlikely that non-specific factors such as motor impairment or enhanced anxiety (Navarro et al. 1997) may contribute to the effects of SR 141716 reported in the present study. Finally, the active doses of SR 141716 to reduce drug-induced hyperactivity in habituated animals were in the range of those found to prevent the main effects of cannabinoid agonists in rats and mice including hypothermia, analgesia, cannabinoid cue (Rinaldi-Carmona et al. 1994; Pério et al. 1996) and to reduce Win 55212-2-induced hyperactivity in gerbils (present study). Thus, hyperactivity produced in habituated animals by drugs known to facilitate dopaminergic (DA) transmission is likely to require activation of endogenous cannabinoid systems. This proposal would be consonant with the reported ability of cannabinoid agonists, given at relatively low dosages, to enhance spontaneous locomotion in rodents (McGregor et al. 1996; present study) and to facilitate DA transmission, especially in mesocorticolimbic dopaminergic systems (Navarro et al. 1993; Gessa et al. 1997, 1998; Tanda et al. 1997).

Several hypotheses can be raised concerning the mechanisms involved in the profoundly different sensitivity to CB1 receptor blockade of drug-induced hyperactivity in habituated versus naive animals.

After habituation, i.e. when response decrement has occurred in association with stimulus satiation, the main effect of cocaine, morphine and amphetamine is less to further enhance ongoing exploratory activity, than to "reinstate" locomotor activity. Interestingly, the doses of stimulant required to enhance locomotion were consistently (3- to 4-fold) lower in habituated versus non-habituated animals, even though the stimulant-induced pattern of locomotion was very similar in both cases. Such a response-reinstating effect may be associated with the drug-induced disruption of attentional processes operating to refrain the animal from responding to irrelevant stimuli as evidenced in various paradigms of information processing including pre-pulse inhibition or latent inhibition (Killcross et al. 1994; Ellenbroek et al. 1996). Reinstatement of behaviour produced by morphine, cocaine and amphetamine might also reflect modifications in the perception of the incentive value of the environment linked to the drug-induced motivational changes. Interestingly, SR 141716 has been shown to counteract the conditioned place preference supported by classical reinforcers including food, cocaine and morphine (Chaperon et al. 1998). Thus, it can be proposed that activation of cannabinoid systems is a required, permissive element in the ability of amphetamine, morphine and cocaine to reinstate behaviour, i.e. to override stimulus satiation. Conversely, cannabinoid activation appeared to have no role in the enhancement of exploratory activity induced by these same drugs in non-habituated animals. Such a proposal is consonant with our observation that Win 55212-2 was more potent and effective in reinstating locomotion in habituated gerbils than to enhance exploratory activity in non-habituated animals. Interestingly, McGregor et al. (1996) reported that the cannabinoid agonist CP 55-940 (at low doses) increased rat locomotor activity mainly during the second half of a 90-min test-session.

Together these data might also suggest that endogenous cannabinoid systems preferentially modulate brain circuits (e.g. mesocortical limbic pathways) involved in cognitive or motivational processes rather than brain structures involved in the mere expression of behaviour (e.g. nigrostriatal pathways). One of the most striking arguments in support of this possibility is the observation (Tanda et al. 1997) that in awake animals with microdialysis probes implanted in the nucleus accumbens, cannabinoid agonists were much more potent in stimulating DA release in the limbic part of the nucleus (shell) than in its striatal subdivision (core). Moreover in rats, SR 141716 was found to stimulate Fos expression in mesocorticolimbic areas including the prefrontal cortex, the ventro-lateral septum, the shell of the nucleus accumbens but not in motor related areas such as the core of the nucleus accumbens and the dorso-lateral part of the caudate putamen (Alonso et al. 1999).

Interestingly, the atypical antipsychotic drug clozapine, which exhibits preferential impact on corticolimbic structures (Robertson et al. 1994) shared with SR 141716 the ability to differentially affect drug-induced reinstatement versus stimulation of locomotion. Indeed, although clozapine (3 mg/kg) was found not to affect Win 55212-2-induced hyperactivity, it abolished morphine- and cocaine-induced hyperactivity in habituated gerbils, whereas it was totally ineffective in non-habituated animals. Conversely, haloperidol was found to reduce drug-induced hyperactivity in habituated and non-habituated gerbils in the same dose range to that producing deleterious effects on spontaneous locomotion in this species.

In conclusion, the results of the present study may have several implications. As distinct from direct DA receptor blockade (classical neuroleptic drugs), but like atypical antipsychotic compounds, inhibition of CB1 receptors may result in dissociating putative motivational and cognitive from motor effects of psychostimulants. This implies that studies designed to investigate antagonism of drug-induced hyperactivity should more systematically consider locomotion of both naive and habituated animals. The antagonistic activity of SR 141716 against the cognition disrupting or reward enhancing properties of drugs such as morphine, amphetamine, cocaine known to provoke or exacerbate schizophrenic

symptomatology suggests that blockade of CB1 receptors could have beneficial effects on this pathology and in particular on cognitive dysfunction.

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