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Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB_1 receptors

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Abstract

The present study was designed to determine if cannabinoids share with other drugs of abuse the ability to stimulate mesolimbic dopaminergic neurons and if this effect is mediated by cannabinoid receptors. To this end, the effects of the prototypical cannabinoid, Δ^9 tetrahydrocannabinol {(−)-trans-(6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol}, and the two highly potent synthetic cannabinoids, {(*R*)-(+)-[2,3-dihydro-5-methyl-3-[(4-morpholinyl)-methyl]pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl,+(1-naphtalenyl)methanone} WIN 55,212-2 and {(−)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)-cicloexan-1-ol} CP 55,940, on the spontaneous discharge rate of meso-accumbens dopamine (A_{10} dopamine) neurons were studied in rats. The intravenous administration of Δ^9-tetrahydrocannabinol, WIN 55,212-2 and CP 55,940 (0.0625–1.0 mg/kg) produced a dose-dependent increase in the spontaneous firing of A_{10} dopamine neurons both in non-anesthetized and anesthetized rats, with a maximal percent increase of 120, 187 and 155 in non-anesthetized and 33, 102 and 52, respectively, in anesthetized rats. The stimulant response to cannabinoids was suppressed by the specific cannabinoid receptor antagonist {*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide} SR 141716A, indicating a cannabinoid receptor-mediated effect. These findings support the contention that cannabinoids regulate mesolimbic dopamine transmission and may help to explain the addictive properties of marijuana. © 1998 Elsevier Science B.V.

Keywords: Dopamine; Ventral tegmental area; Drug abuse; Electrophysiology; Cannabinoid

1. Introduction

The mechanism of the euphoriant and addictive effects of marijuana is still unknown, despite the advances made in cannabinoid research during the last few years. These include the demonstration of a central (CB_1) (Devane et al., 1988) and a peripheral (CB_2) (Munro et al., 1993) cannabinoid receptor, their cloning (Matsuda et al., 1990), the discovery of anandamide, an endogenous putative cannabinoid agonist (Devane et al., 1992), and the synthesis of highly potent and selective cannabinoid receptor agonists (Johnson and Melvin, 1986; D'ambra et al., 1992) and antagonists (Rinaldi-Carmona et al., 1994; Pertwee et al., 1995). These discoveries, together with recent advances in the neurobiology of drugs of abuse, have generated important information and powerful means to investigate the elusive problem of why marijuana is so widely abused.

Experimental evidence indicates that the mesolimbic dopamine system is the common neuronal substrate for the motivational and rewarding properties of drugs of abuse. Indeed, prototypical drugs of abuse such as morphine (Matthews and German, 1984), alcohol (Mereu et al., 1984a) and nicotine (Mereu et al., 1987) increase the discharge rate of mesolimbic dopamine neurons and such activation is associated with increased dopamine output in the innervated areas (Di Chiara and Imperato, 1988). Although cocaine may appear as an exception to this general rule (Einhorn et al., 1988), it increases dopamine output by virtue of its dopamine transporter-blocking properties (Giros et al., 1996). A number of studies suggest that {(−)-trans-(6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol} (Δ^9-tetrahydrocannabinol), the psychoactive principle of marijuana, also facilitates mesolimbic dopamine neurotransmission

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and that this effect may play a role in the reinforcing properties of the drug.

Thus, Δ^9-tetrahydrocannabinol has been shown to facilitate brain stimulation reward in the medial forebrain bundle at doses within a range pharmacologically relevant to human recreational marijuana use (Gardner et al., 1988). It augments potassium-stimulated striatal dopamine efflux in the anesthetized rat (Ng Cheong Ton et al., 1988) and enhances dopamine output in both the nucleus accumbens and medial prefrontal cortex (Gardner and Lowinson, 1991) in freely moving rats as measured by microdialysis. However, negative results have also been reported (Castañeda et al., 1991).

The stimulant effect of Δ^9-tetrahydrocannabinol on dopamine outflow in vivo has been attributed to the inhibition of dopamine uptake and/or the facilitation of dopamine release by nerve terminals (Sakurai Yamashita et al., 1989). A direct action of Δ^9-tetrahydrocannabinol on dopamine nerve endings, however, seems to be ruled out because cannabinoid receptors appear not to be localized on dopamine neurons (Herkenham et al., 1994); moreover the effective concentrations of Δ^9-tetrahydrocannabinol found to facilitate dopamine release or to inhibit dopamine uptake in synaptosomes are much higher than those reached in the brain after systemic administration of pharmacologically active doses of Δ^9-tetrahydrocannabinol, at least in the rat. In contrast, low concentrations of Δ^9-tetrahydrocannabinol have been shown to produce opposite effects, namely they stimulate dopamine uptake and inhibit dopamine release in the synaptosomal preparation (Poddar and Dewey, 1980). These considerations suggest that the effects of Δ^9-tetrahydrocannabinol on mesolimbic dopamine system are complex and may represent the end-point of different actions at multiple levels.

In spite of the great number of behavioral (Anderson et al., 1995; Sañudo-Peña et al., 1996) and biochemical (Dewey, 1986) studies on Δ^9-tetrahydrocannabinol interaction with dopamine systems, there have been no electrophysiological investigations. In an effort to elucidate the actions of exogenously applied cannabinoids on mesolimbic dopamine neuronal function, we have begun a series of experiments, using different molecules with proven cannabinoid activity, in both non anesthetized and anesthetized rats in order to gain some further insight into the interactions between the effects observed and anesthetic used and/or stress produced by muscle relaxants. In a preliminary report (Melis et al., 1996), we described the dose-dependent stimulation produced by intravenous administration of {(*R*)-(+)-[2,3-dihydro-5-methyl-3-[(4-morpholinyl)-methyl]pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl, (1-naphtalenyl)methanone} (WIN 55,212-2) on antidromically-identified mesolimbic dopamine neurons. More recently (French et al., 1997), this effect has been confirmed (at least under chloral-hydrate anesthesia) and extended to Δ^9-tetrahydrocannabinol (French et al., 1997).

To further explore these issues, we report here the effect on dopaminergic neuronal function of the prototypical cannabinoid Δ^9–tetrahydrocannabinol and the two highly potent synthetic cannabinoids WIN 55,212-2 and {(−)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)-cicloexan-1-ol} CP 55,940 under different experimental conditions such as chloral hydrate-induced anesthesia and succinylcholine induced immobilization. In addition, we describe the blocking effect exerted by the cannabinoid CB_1 receptor antagonist compound {*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide} (SR141716A) on the stimulation induced by the three cannabinoid agonists and its lack of action when administered alone.

2. Materials and methods

Male Sprague–Dawley albino rats (200–300 g) were used in all experiments. All subjects were kept on a 12 h/12 h light/dark cycle with food and water available ad libitum. Experimental protocols were approved by the Ethics Committee at the University of Cagliari and performed in strict accordance with E.C. regulations for the use of experimental animals (CEE No. 86/609).

2.1. Non-anesthetized rats

Subjects were temporarily anesthetized with halothane/room air inhalation anesthesia and the femoral vein was cannulated for intravenous administration of pharmacological agents. The trachea was then exposed and incised to allow tracheal intubation with a teflon catheter for artificial respiration.

Succinylcholine chloride (20 mg/kg) was administered intravenously and once muscular paralysis was obtained the rat was placed in a stereotaxic apparatus (Kopf) and the tracheal catheter was connected to a mechanical rodent ventilator (7025 Stoelting) set to deliver 90 strokes/min (3 ml/stroke). All incision and pressure points were infiltrated with a 2% solution of xylocaine and supplemented as needed. Body temperature was maintained constant at 38 ± 1°C by means of an electrically controlled heating pad.

2.2. Anesthetized rats

Rats belonging to this group were anesthetized with chloral hydrate (400 mg/kg) i.p. and the femoral vein was cannulated for intravenous administration of pharmacological agents. Thereafter, non-anesthetized (succinylcholine-treated) and chloral hydrate anesthetized rats were prepared as follows: the scalp was retracted and two burr holes were drilled: one for the placement of a recording electrode above the ventral tegmental area (AP 1.8–2.0; L 0.1–1.2 from lambda), and the other to introduce a Formvar coated stainless-steel bipolar electrode (250 μm tip diameter) into the nucleus accumbens (AP 8.8 from lambda;

L 1.6 from midline; V 7.1 from dura matter) for antidromic identification. Stimuli consisting of monophasic rectangular pulses (0.1–2.0 mA; 0.1–0.5 ms; 0.8 Hz) were generated by a Grass Instrument stimulator (S88) and stimulus isolation unit (SIU5).

The stimulating current was monitored on the oscilloscope. Dopamine neurons were identified according to well established electrophysiological characteristics including antidromic activation from the nucleus accumbens and collision of an antidromically elicited spike with spontaneously occurring action potentials (Lipsky, 1981).

Δ^9-Tetrahydrocannabinol, in ethanol solution, was purchased from Research Biochemicals International (Natick, MA). The ethanol was evaporated immediately before use under argon gas and the residue was emulsified, as were the other cannabinoids, in 1% Tween 80 and then diluted in a saline solution. Drugs were injected i.v. in a volume of 1 ml/kg.

The basal firing rate was recorded for 5 min and cannabinoids were administered i.v. at exponentially increasing doses (0.0625–1 mg/kg) at 120 s intervals. Changes in firing rate were calculated by averaging the effects of the drug for the two minutes after drug administration and comparing them to the mean of the pre-drug baseline. Only one cell was recorded per rat. The firing pattern was analyzed using a Commodore 128 computer programmed in machine language as already described (Diana et al., 1989).

Statistical significance of the data was evaluated by using two-way analysis of variance (ANOVA) followed by Student–Newman–Keuls' test. Burst data were analyzed by using Student *t*-test.

3. Results

Initial experiments were carried out in non-anesthetized rats. The choice of this preparation was based on the fact that general anesthetics have been shown to modify both the spontaneous firing rate of dopamine neurons and their response to different drugs (Mereu et al., 1984b; Kelland et al., 1989; Kelland et al., 1990). To reduce pain, one of the main inconveniences of this preparation, pressure points and surgical wounds were locally anesthetized with xylocaine (see above).

As shown in Fig. 1 the i.v. administration of Δ^9-tetrahydrocannabinol ($n = 13$), WIN 55,212-2 ($n = 13$) and CP 55,940 ($n = 6$) to non-anesthetized rats produced a dose-related and long-lasting (> 20 min) increase in the spontaneous firing rate of A_{10} dopamine neurons. Basal firing rates were 2.44 ± 0.53; 2.82 ± 0.54; 3.13 ± 0.61 Hz for Δ^9-tetrahydrocannabinol, WIN 55,212-2 and CP 55,940 groups, respectively.

Following the highest dose tested, a maximal increase of 120, 187 and 155%, respectively, was observed [$F(5,72) = 3.64$, $P < 0.05$; $F(5,72) = 12.21$, $P < 0.01$; $F(4,50) = 8.62$, $P < 0.00005$]. Cannabinoid-induced stimulation of firing rate was associated with a parallel increase in bursting activity (Fig. 3). The stimulant response induced by cannabinoids was abruptly suppressed by the i.v. administration of 1 mg/kg of the specific cannabinoid antagonist SR 141716A (Fig. 2).

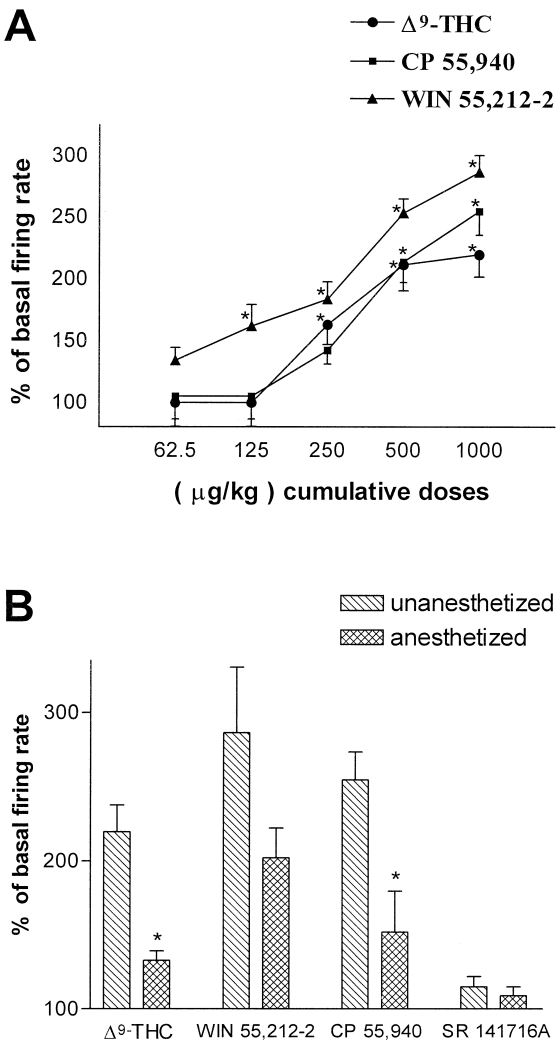

Fig. 1. (A) Dose–response curves depicting the stimulating effect (ANOVA, see Section 3) of cumulative doses of cannabinoids on the firing rate of antidromically identified A_{10} dopamine neurons in non-anesthetized rats. Data (mean ± S.E.M.) are expressed as percentages of the basal firing rate. $^*P < 0.01$ with respect to pre-drug level (Newman–Keuls' test). (B) Effect of chloral hydrate anesthesia on cannabinoid-induced stimulation of A_{10} dopamine neurons. Each column represents the effect observed with the highest cumulative dose administered (1 mg/kg i.v.) and is expressed as the percentage of the basal firing rate (mean ± S.E.M.). $^*P < 0.0001$ with respect to the corresponding non-anesthetized group (Newman–Keuls' test).

As previously reported (Gueudet et al., 1995), SR 141716A per se did not significantly change the spontaneous firing rate of dopamine neurons, suggesting that endogenous cannabinoids do not tonically control the activity of these neurons.

Cannabinoids were still effective in stimulating the

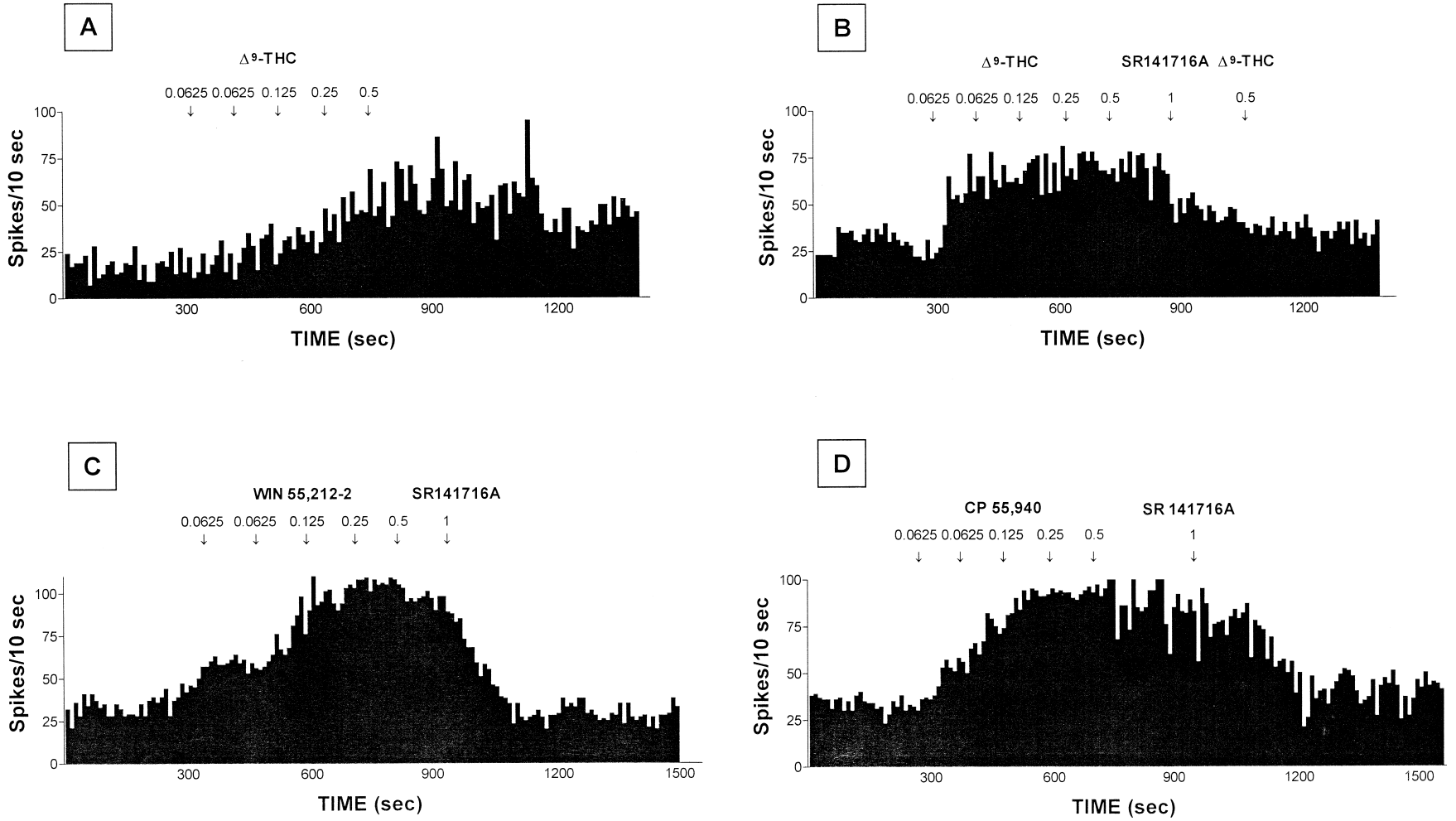

Fig. 2. Examples of the effect produced by cumulative doses of Δ^9-tetrahydrocannabinol (A, B), WIN 55,212-2 (C) and CP 55,940 (D) on antidromically identified A_{10} dopamine neurons recorded from non-anesthetized rats and its reversal induced by SR 141716A (B, C, D). Arrows indicate time of injection. Numbers above arrows indicate dosages expressed in mg/kg iv. Note that in (A) the Δ^9-tetrahydrocannabinol-induced increase in firing rate lasted for as long as the recordings were made (20 min) and in (B) agonist administration after the antagonist was without effect.

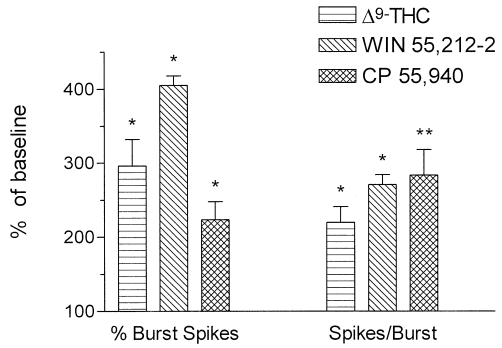

Fig. 3. Effect of cannabinoids on the burst firing of A_{10} dopamine neurons in non-anesthetized rats. All effects were observed with the highest cumulative dose administered (1 mg/kg i.v.) and expressed as the percentage of the baseline (mean ± S.E.M.). $^{*}P < 0.01$ and $^{**}P < 0.05$ with respect to pre-drug level (Student's *t*-test).

electrical activity of A_{10} dopamine neurons in chloral hydrate-anesthetized rats, but their effect was significantly reduced with respect to that in the non-anesthetized rats [Δ^9-tetrahydrocannabinol: $F(1,43) = 29.59$, $P < 0.000005$; $F(4,43) = 13.36$, $P = 0.00000$; $F(4,43) = 6.51$, $P < 0.0005$; WIN 55,212-2: $F(1,50) = 1.57$, $P = 0.21$; $F(4,50) = 7.71$, $P < 0.0001$; $F(4,50) = 1.33$, $P = 0.26$; CP 55,940: $F(1,50) = 10.688$, $P < 0.005$; $F(4,50) = 8.62$, $P < 0.00005$; $F(4,50) = 2.27$, $P = 0.07$], the maximal stimulation being 33, 102 and 52% after Δ^9-tetrahydrocannabinol, WIN 55,212-2 and CP 55,940 respectively (Fig. 1B). Basal firing rates were 3.28 ± 0.29; 2.74 ± 0.67; 3.22 ± 0.68 for Δ^9-tetrahydrocannabinol, WIN 55,212-2 and CP 55,940 respectively.

4. Discussion

These results confirm and extend previous findings (Melis et al., 1996; French et al., 1997) which showed that Δ^9-tetrahydrocannabinol (French, 1997) and WIN 55,212-2 (Melis et al., 1996; French et al., 1997) increase the firing of A_{10} dopamine cells under chloral hydrate anesthesia. This effect, which is extended by the present study to non anesthetized animals, is most likely mediated via cannabinoid receptors, being (i) mimicked by another structurally distinct cannabinoid agonist such as CP 55,940; (ii) restricted to the active enantiomer of WIN 55,212-2 (French et al., 1997) and, (iii) suppressed by the specific CB_1 receptor antagonist, SR 141716A (French, 1997), which by itself was ineffective (Gueudet et al., 1995). This latter observation would tend to exclude the possibility of a tonically active input exerted by endogenous cannabinoids on dopamine neurons of the mesolimbic system.

Since the cannabinoids were administered systemically, their exact site of action in the activation of dopamine neurons remains unclear. Cannabinoid CB_1 receptors are not localized on dopamine cell bodies or in their nerve terminals (Herkenham et al., 1994), and it is therefore unlikely that cannabinoids directly stimulate dopamine cells; however, they might influence dopamine neurons through a multisynaptic neuronal circuit by acting on the postsynaptic targets in the basal ganglia, where cannabinoid CB_1 receptors are heavily concentrated (Herkenham et al., 1994).

The effects observed under anesthesia and immobilization were qualitatively similar but quantitatively different. The 'dumping' effect of general anesthesia on cannabinoid-induced stimulation of A_{10} dopamine neurons might be due to a reduced functionality of forebrain–midbrain connections where dopamine neurons have their cell bodies. Accordingly, general anesthetics have been shown to reduce the stimulant effect of various compounds on dopamine neurons (Mereu et al., 1984b; Kelland et al., 1989; Kelland et al., 1990).

In conclusion, the present results indicate that Δ^9-tetrahydrocannabinol and other cannabinoids, such as WIN 55,212-2 and CP 55940, increase the activity of dopamine neurons in the mesolimbic system through activation of cannabinoid CB_1 receptors, as demonstrated by the blockade of these effects by the cannabinoid CB_1 receptor antagonist SR 141716A, irrespective of the anesthetic or immobilizing agent used.

Thus, cannabinoids resemble other major drugs of abuse such as ethanol, nicotine and morphine, in producing, as a final common neuronal action, facilitation of the mesolimbic dopamine system.

Since cannabinoid effects were achieved within a range of doses that are believed to be pharmacologically relevant to human marijuana use, dopamine stimulation may contribute to the euphorigenic properties and abuse liability of this drug. This in turn, may highlight, once again, the pivotal role played by the mesolimbic dopaminergic system in conveying the acute rewarding properties of addicting drugs of different chemical classes.

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