Perspectives in Pharmacology

Cannabinoid CB₁ Receptor Antagonists as Promising New Medications for Drug Dependence

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ABSTRACT

This review examines the development of cannabinoid CB₁ receptor antagonists as a new class of therapeutic agents for drug addiction. Abused drugs [alcohol, opiates, Δ⁹-THC, and psychostimulants, including nicotine] elicit a variety of chronically relapsing disorders by interacting with endogenous neural pathways in the brain. In particular, they share the common property of activating mesolimbic dopamine brain reward systems, and virtually all abused drugs elevate dopamine levels in the nucleus accumbens. Cannabinoid CB₁ receptors are expressed in this brain reward circuit and modulate the dopamine-releasing effects of Δ⁹-THC and nicotine. Rimonabant (SR141716), a CB₁ receptor antagonist, blocks both the dopamine-releasing and discriminative and rewarding effects of Δ⁹-THC in animals. Blockade of CB₁ receptor activity by genetic invalidation also decreases rewarding effects of opiates and alcohol in animals. Although CB₁ receptor blockade is generally ineffective in reducing the self-administration of cocaine in rodents and primates, it reduces the reinstatement of extinguished cocaine-seeking behavior produced by cocaine-associated conditioned stimuli and cocaine-priming injections. Likewise, CB₁ receptor blockade is effective in reducing nicotine-seeking behavior induced by re-exposure to nicotine-associated stimuli. Some of these findings have been recently validated in humans. In clinical trials, Rimonabant blocks the subjective effects of Δ⁹-THC in humans and prevents relapse to smoking in exsmokers. Findings from both clinical and preclinical studies suggest that ligands blocking CB₁ receptors offer a novel approach for patients suffering from drug dependence that may be efficacious across different classes of abused drugs.

CB₁ Receptors Modulate the Brain Reward Pathway

Drug dependence is a chronic, relapsing disorder in which compulsive drug-seeking and -taking behavior persists despite serious negative consequences (American Psychiatric Association, 2000). Addictive substances, such as cannabinoids, opioids, ethanol, and psychostimulants, including nicotine, induce pleasant states or relieve distress, effects that contribute to their recreational use. After repeated exposure, adaptive changes occur in the central nervous system that lead to drug dependence (American Psychiatric Association, 2000). Although addictive drugs produce their effects through actions at various receptors in the brain, it is thought that their common effects on the activity of dopaminergic brain reward pathways is primarily responsible for their addictive properties (Koob, 1992a,b; Wise, 2004). Notably, the mesocorticolimbic system, which projects from the ventral tegmental area to the nucleus accumbens, cortical areas, and amygdala, is implicated in the rewarding effects of psychostimulants and other drugs of abuse, as well as the effects of nondrug natural rewards such as food (Wise, 1982). The involvement of dopamine in the rewarding effects of drugs of abuse is suggested by findings that most drugs abused by humans increase levels of dopamine in the nucleus.
accumbens (Imperato et al., 1986; Pidoplichko et al., 1997) and that blockade of dopamine transmission reduces the rewarding effects of psychostimulants (Koob, 1992a,b); however, the role of dopamine seems more complex than simply mediating the primary reinforcing effects of drugs of abuse (Salamone et al., 2003; Wise, 2004). Recent evidence suggests that dopamine is strongly implicated in learning and conditioning processes (Schultz et al., 1997; Schultz, 2002) and in drug-seeking behavior (Phillips et al., 2003).

Marijuana is the most widely used illicit drug in the United States. The main psychoactive ingredient in marijuana is Δ⁹-tetrahydrocannabinol (Δ⁹-THC). Two forms of cannabinoid receptors, CB₁ and CB₂, have been cloned (Matsuda et al., 1990; Gerard et al., 1991; Munro et al., 1993). The CB₁ receptor and its splice variant, the CB₁Δ₅ receptor, are predominantly found in the brain, with the highest density in the hippocampus, cerebellum, cortex, and striatum, whereas CB₂ receptors are located peripherally, principally associated with the immune system (Howlett et al., 2002). New data suggest the existence of an additional cannabinoid receptor (non-CB₁/non-CB₂) (see Wilson and Nicoll, 2002). Δ⁹-THC may produce its effects by duplicating the effects of natural ligands for CB₁ receptors (anandamide, 2-arachidonylglycerol, and, perhaps, noladin ether), which have a shorter duration of action than synthetic or plant-derived cannabinoids and are implicated in various nervous system functions such as reward, memory, cognition, and pain perception (Wilson and Nicoll, 2002). Central nervous system effects produced by Δ⁹-THC have been linked to the cannabinoid CB₁ receptor. As with other drugs of abuse, Δ⁹-THC also produces an elevation in dopamine levels in the nucleus accumbens of rats (Chen et al., 1990) that is blocked by SR141716, a cannabinoid CB₁ receptor antagonist (Tanda and Di Chiara, 1997).

The potential utility of cannabinoid CB₁ receptor antagonists for the treatment of drug dependence has recently received considerable attention. This approach has been tested for Δ⁹-THC and other types of drugs of abuse. This review focuses on the development of cannabinoid CB₁ receptor antagonists for the treatment of drug dependence. We will first summarize the main animal models used to assess subjective and rewarding/reinforcing effects of drugs of abuse and then summarize in Table 1 the preclinical and clinical findings related to CB₁ receptor blockade and the subjective and rewarding/reinforcing effects of different drugs of abuse in these models. The results obtained with various drugs of abuse will be presented by drug class. The putative neurobiological mechanisms underlying these effects will also be discussed. Although some drugs of abuse, such as ecstasy, are sometimes used together with marijuana (Croft et al., 2001), the involvement of cannabinoid mechanisms in the effects of these drugs has seldom been studied (Braida and Sala, 2002), and these limited findings will not be reviewed here.

**Animal Models for Studying Effects of Drugs of Abuse**

A variety of animal models are available to study the cardinal features of drug dependence (Schuster and Woods, 1968; Goldberg, 1975; Goldberg et al., 1975, 1979, 1981; Spealman and Goldberg, 1978; Katz and Goldberg, 1988; Markou et al., 1993; Everitt and Robbins, 2000; Schindler et al., 2002; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). The effects of CB₁ blockade have been evaluated using animals models for the subjective effects of drugs (drug discrimination), their rewarding/reinforcing properties [intravenous drug self-administration, conditioned place preference (CPP), and intracranial self-stimulation procedures], the influence of environmental factors on drug-seeking behavior (CPP, second-order schedules of drug self-administration, reinstatement of extinguished drug-seeking behavior, and other relapse models), and the withdrawal states associated with the abrupt termination of drug action (administration of selective antagonists after chronic exposure). We will mainly review results obtained with the drug discrimination procedure and the two most widely used procedures assessing rewarding or reinforcing effects of drugs in experimental animals: intravenous drug self-administration and drug-induced CPP procedures.

**Drug Discrimination**

Humans that abuse psychoactive drugs report characteristic subjective effects, and drug discrimination procedures in rats and monkeys are extensively used as animal models for subjective reports of drug effects in humans. The organism’s ability to perceive and identify the characteristic interoceptive effects of drugs is thought to play a role in drug seeking, encouraging the development of this behavior and directing it toward one substance rather than another on the basis of relative potencies and effects (Stoelerman and Shoaib, 1991). These interoceptive subjective effects of drugs are most frequently assessed in humans through the use of performance-assessment tasks and subject-rating scales. In animals, the interoceptive effects of drugs can serve as discriminative stimuli to indicate how to obtain a reinforcer such as a food pellet or how to avoid an electric shock. For this purpose, animals are trained under a discrete trial schedule of food pellet delivery or stimulus-shock termination to respond on one lever after an injection of a training dose of a drug and on the other lever after an injection of vehicle. Once animals learn to reliably make this discrimination, the subjective effects of different drugs can be compared, and the modulation of subjective effects of drugs of abuse by various pharmacological ligands can be measured.

**Intravenous Drug Self-Administration**

Natural rewards, such as water or food, and drugs of abuse may serve as positive reinforcers. For example, to assess the reinforcing effects of food, a food-deprived animal can be placed in a sound-attenuating chamber containing stimulus lights, response levers, and a device for dispensing food pellets automatically. Lever-pressing responses will occur with increasing frequency when they result in delivery of the food pellets, which, therefore, serve as positive reinforcers under these conditions. With intravenous drug self-administration procedures, a catheter implanted in a jugular vein allows the animal to intravenously self-administer a small amount of drug by pressing a lever. The administration of drug constitutes the event that positively reinforces the lever-pressing behavior, and reward is inferred if the frequency of responding subsequently increases (thus defining reinforcement). With these behavioral procedures, a stimulus light is often associated with delivery of the reinforcer. This stimulus, or cue, progressively gains motivational value by Pavlovian con-
ditioning and can induce and maintain drug-seeking behavior and also reinstate drug-seeking behavior after extinction (Goldberg, 1975; Goldberg et al., 1975, 1983; de Wit and Stewart, 1981; Stewart, 1983; Self and Nestler, 1988; Meil and See, 1996; Arroyo et al., 1999), providing useful measures of the motivational effects of drug-related stimuli. Various schedules of reinforcement of drug self-administration behavior have been developed.

Under a fixed ratio (FR) schedule of intravenous drug injection, a fixed number of lever presses is necessary to obtain each injection of drug (e.g., one lever press for a fixed ratio 1, i.e., FR1, schedule). In contrast, under a progressive ratio schedule, the number of lever-press responses necessary to obtain a drug injection increases after each drug injection (Hodos, 1961). Thus, the number of responses the subject must make for each successive drug injection (the ratio value) is increased progressively until the subject fails to emit the required number of responses; this highest ratio (the “breaking point”) is thought to reflect the reinforcing effectiveness of the drug. Self-administration studies have repeatedly shown that most drugs considered to be addictive in humans can serve as positive reinforcers for laboratory rats and monkeys, whereas nonaddictive drugs have given negative results in most cases (Katz and Goldberg, 1988; Balster, 1992). Once an animal has been trained to self-administer the drug, the influences of drug priming, stressors, or presentation of drug-associated cues on drug self-administration behavior or relapse to extinguished drug-seeking behavior provide useful measures for studying drug taking or relapse (Shalev et al., 2002).

**Drug-Induced Conditioned Place Preferences**

Another experimental animal model for exploring the rewarding effects of drugs of abuse is the CPP procedure. A distinctive environment (e.g., one compartment of a two- or three-compartment apparatus) is paired repeatedly with the administration of a drug, and a different environment is repeatedly associated with the administration of vehicle. CPP occurs when repeated administration of a drug in this particular environment results in the ability of that environment to elicit approach behavior and increased time contact (place preference) in the absence of the previously administered drug. It has been argued that CPP, like drug self-administration and a number of related phenomena, is an example of dopamine-mediated incentive learning and that

### TABLE 1

Main effect of CB1 blockade on the subjective, discriminative, and rewarding/reinforcing effects of drugs of abuse in animal and human subjects

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<tr>
<td>Rats</td>
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<td>Mice</td>
<td>Self-administration of i.v. nicotine at a low ratio requirement (FR1)</td>
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</table>
the approach behavior and increased time spent by animals in a drug-paired environment can be considered a measure of drug-seeking behavior (Bardo and Bevins, 2000; Le Foll and Goldberg, 2004a). CPP have been demonstrated for most drugs of abuse, as well as natural rewards such as food. The acquisition of a drug-induced CPP is likely to reflect the rewarding properties of a drug of abuse, whereas its expression reflects the influence on behavior of environmental stimuli previously associated with a drug’s effects.

Effects of CB₁ Blockade on Effects of Drugs of Abuse

Δ⁹-Tetrahydrocannabinol

Since the development of a rodent model of Δ⁹-THC self-administration has so far been unsuccessful (Tanda and Goldberg, 2003), the drug discrimination model has been widely used to study cannabinoid effects in animals. Animals can learn to reliably discriminate Δ⁹-THC from vehicle, and the cannabinoid CB₁ antagonist SR141716 produces reversible, dose-dependent antagonism of the discriminative stimulus effects of Δ⁹-THC in rats (Wiley et al., 1995; Jarbe et al., 2001; Solinas et al., 2003) and monkeys (Wiley et al., 1995). When SR141716 was administered alone, it did not substitute for Δ⁹-THC in rats (Wiley et al., 1995). Moreover, in humans, SR141716 (Rimonabant) was also able to block subjective effects induced by Δ⁹-THC (Huestis et al., 2001). This selective cannabinoid antagonist also precipitated a withdrawal syndrome in cannabinoid-dependent animals (Tanda et al., 1999; Maldonado and Rodriguez de Fonseca, 2002).

The precipitation of a physical withdrawal syndrome by SR141716 was associated with a reduction of dopamine levels in the shell of the nucleus accumbens in cannabinoid-dependent rats, but no such effects were found after the administration of SR141716 to saline-control rats (Tanda et al., 1999). Recently, a squirrel monkey model of Δ⁹-THC intravenous self-administration has been developed (Tanda et al., 2000; Justinova et al., 2003). SR141716 almost entirely blocked the self-administration of Δ⁹-THC in squirrel monkeys under an FR10 schedule of reinforcement (Tanda et al., 2000). These results suggest that blockade of cannabinoid CB₁ receptors may block both the subjective and rewarding effects of Δ⁹-THC in humans.

Opiates

Functional interactions between cannabinoid and opioid neurotransmitter systems that are implicated in drug reinforcement/reward processes (Navarro et al., 2001; De Vries et al., 2003; Solinas et al., 2003) have been described previously (Manzanares et al., 1999). Notably, the discriminative (Solinas et al., 2004) and rewarding/reinforcing (Chen et al., 1990; Justinova et al., 2004) effects of Δ⁹-THC are reversed by treatment with the opioid receptor antagonists naloxone and naltrexone. Selective µ-opioid receptor inhibition in mice also reduced the rewarding effects of Δ⁹-THC, as assessed by the conditioned place preference procedure (Ghozland et al., 2002). These effects seem specific to the rewarding/reinforcing effects of Δ⁹-THC, since naltrexone, an opiate antagonist, did not block the subjective effects of Δ⁹-THC administration in humans (Wachtel and de Wit, 2000; Haney et al., 2003). Conversely, several studies have evaluated cannabinoid system modulation of the reinforcing effects of opiates. SR141716 treatment prevented the development of morphine-induced CPP (Chaperon et al., 1998), and cannabinoid CB₁ receptor knockout mice did not self-administer morphine (Cosset al., 2001) or develop morphine-induced CPP (Martin et al., 2000). In agreement, blockade of cannabinoid CB₁ receptors by SR141716 markedly reduced responding for intravenous heroin injections under an FR5 schedule of reinforcement and to a greater extent under a progressive ratio schedule of reinforcement in rats (De Vries et al., 2003; Solinas et al., 2003). The cannabinoid CB₁ receptor agonist HU-210 reinstated heroin-seeking behavior following a 2-week extinction period, whereas SR141716 dose-dependently attenuated heroin seeking produced by a priming injection of heroin or re-exposure to heroin-associated stimuli (De Vries et al., 2003). Although SR141716 markedly decreased responding for heroin by rats under a progressive ratio schedule across a wide range of heroin doses, it had little effect on responding for food under a similar progressive ratio schedule (Solinas et al., 2003). In contrast to effects under the progressive ratio schedule, when responding was continuously reinforced under an FR1 schedule, SR141716 only reduced responding for low 12.5- and 25-µg/kg injection doses of heroin. The fact that heroin self-administration was affected in a different manner under these schedules is consistent with a behavioral economic analysis (Bickel et al., 2000), where the price of drug is considered to be the amount of effort (ratio size) required to obtain a fixed amount of drug. Thus, the effects of SR141716 on drug self-administration were more pronounced under a progressive ratio schedule of reinforcement (high price of drug), weaker under an FR5 schedule of self-administration (lower price of drug), and null under an FR1 schedule of self-administration of heroin or cocaine injections (very low price of drug). The effectiveness of cannabinoid CB₁ receptor blockade seems to depend on the price of the drug, with self-administration at high drug prices being notably sensitive to disruption. It is interesting to note that SR141716 did not modify the dopamine-releasing effect of heroin in the nucleus accumbens (Tanda and Di Chiara, 1997; Caille and Parsons, 2003).

Psychostimulants (Cocaine-Amphetamine)

Several experiments do not support, at first sight, an involvement of cannabinoid systems in the reinforcing effects of psychostimulants. CB₁ receptor-deficient mice learned to self-administer cocaine and amphetamine, as did their wild-type littermate controls (Cosset al., 2001). Moreover, SR141716 administration did not interfere with cocaine self-administration in rats (De Vries et al., 2001) or monkeys (Tanda et al., 2000) trained under fixed ratio schedules of reinforcement (Fig. 1). This lack of effect of SR141716 did not reflect an insufficient dosage, since the doses of SR141716 tested were able to dramatically reduce Δ⁹-THC self-administration in monkeys (Tanda et al., 2000) (Fig. 1). In contrast, AM-251, another CB₁ receptor antagonist, decreased the frequency of methamphetamine self-administration under a fixed ratio schedule in rats (decreased drug intake), whereas anandamide and R-methanandamide, two cannabinoid receptor agonists, tended to increase the frequency of methamphetamine self-administration (Vinklerova et al., 2002). SR141716 was also effective in blocking the acquisition, but not the expression, of cocaine-induced CPP (Chaperon et al., 1998). However, CB₁ receptor invalidation did not prevent the development of cocaine-induced CPP (Martin et al., 2000). These studies suggest a weak modulatory role of en-
docannabinoids on intake and, perhaps, on the rewarding/reinforcing effects of psychostimulants. The influence of the cannabinoid system on relapse has been demonstrated more clearly (De Vries et al., 2001). SR141716 reduced relapse to cocaine-seeking behavior produced by cocaine-paired stimuli (cues) (De Vries et al., 2001) (Fig. 1), whereas HU-210, a CB1 receptor agonist, precipitated relapse to cocaine-seeking behavior (De Vries et al., 2001). Blockade of CB1 receptors by SR141716 also was able to block relapse to cocaine-seeking behavior produced by a priming injection of cocaine but not by environmental stressors (De Vries et al., 2001). Likewise, SR141716 blocked the reinstatement of methamphetamine-seeking behavior in rats (Anggadiredja et al., 2004). Further experiments are needed to clarify the involvement of endogenous cannabinoid systems in the rewarding/reinforcing effects of psychostimulants.

Ethanol

Although the sites of actions for ethanol's effects in the brain are poorly understood, ethanol's reinforcing effects seem to involve dopamine pathways (Tabakoff and Hoffman, 1996). Recent evidence suggests that some of the pharmacological and behavioral effects of ethanol may also be mediated by endocannabinoid systems (Hungund et al., 2002). The expression of cannabinoid CB1 receptors and their coupling to G proteins, as shown by the guanosine 5'-O-\([\text{35S}]\text{thio}\)triposphate binding assay, seems to be different between alcohol-prefering and -avoiding mice (Hungund and Basavarajappa, 2000; Basavarajappa and Hungund, 2001). The pharmacological results obtained with SR141716 have been more pronounced with ethanol than with opiates and psychostimulants. Blockade of cannabinoid CB1 receptors reduced alcohol intake (Arnone et al., 1997; Colombo et al., 1998; Rodriguez de Fonseca et al., 1999; Rinaldi-Carmona et al., 2004). The oral consumption of beer by rats, as assessed by a lick-based progressive ratio procedure, was decreased by CB1 receptor blockade and increased by CB1 receptor stimulation (Gallate and McGregor, 1999; Gallate et al., 1999, 2004). These effects have been reproduced in mice (Poncelet et al., 2003). The involvement of cannabinoid CB1 receptors in the reinforcing/rewarding effects of ethanol is further indicated by findings that ethanol consumption is reduced in CB1 receptor-deficient mice (Hungund et al., 2003; Poncelet et al., 2003; Naassila et al., 2004) and that the effects of SR141716 are abolished in these CB1 receptor-deficient mice (Poncelet et al., 2003). Moreover, CB1 receptor invalidation reduces ethanol-induced CPP (Houchi et al., 2004). All of these converging findings suggest that cannabinoid CB1 receptor blockade may be an effective approach to the treatment of alcohol dependence in humans.

Nicotine

Nicotine and Δ⁹-THC (in the form of marijuana) are often used in combination by humans. Several interactions have been described between nicotine and Δ⁹-THC in animals (Valjent et al., 2002). Notably, the rewarding effects of these
two drugs measured by the CPP paradigm were additive when administered together; subthreshold doses of nicotine and Δ9-THC, which were ineffective in inducing CPP by themselves, induced significant CPP when given together (Valjent et al., 2002). Interestingly, the cannabinoid CB1 receptor antagonist SR141716 decreased nicotine self-administration in rats (Cohen et al., 2002), and nicotine was not able to induce conditioned place preferences in CB1 receptor-deficient mice compared with their wild-type littermates (Castane et al., 2002). In contrast, CB1 receptor knockout mice did seem to learn to self-administer nicotine (Cossu et al., 2001), suggesting that some of the actions of nicotine are not affected by cannabinoid CB1 receptor blockade. Blockade of CB1 receptors by SR141716 also did not block the discriminative stimulus effects of a high 0.4-mg/kg training dose of nicotine in one study (Cohen et al., 2002) and failed to change the discriminative stimulus effects of doses of nicotine ranging from 0.01 to 0.6 mg/kg in another study (Le Foll and Goldberg, 2004b). Interestingly, SR141716 dose-dependently blocked the dopamine-releasing effects of nicotine in the nucleus accumbens (Cohen et al., 2002) and the dopaminergic component of the nicotine discrimination (Cohen et al., 2002).

Since dopamine release in the nucleus accumbens is thought to play a major role in the positive reinforcing effects of nicotine, these findings support a role for cannabinoid CB1 receptors in modulating the rewarding/reinforcing effects of nicotine.

The maintenance of nicotine self-administration behavior in rats and monkeys often seems to critically depend on associated environmental stimuli (Goldberg et al., 1981; Caggiula et al., 2001; Cohen et al., 2004), and persistent effects of conditioned environmental stimuli previously associated with the effects of nicotine in tobacco may be a major determinant of relapse to smoking behavior in exsmokers. Acute administration of SR141716 blocks the expression of nicotine-induced conditioned place preferences in rats (Le Foll and Goldberg, 2004b) (see Fig. 2) and the influence of environmental stimuli on nicotine-seeking behavior (Cohen et al., 2004). These findings suggest that cannabinoid CB1 receptor blockade reduced the effectiveness of conditioned motivational stimuli associated with nicotine injection. In agreement with this hypothesis, SR141716 administration has been shown to reduce intravenous nicotine self-administration behavior in rats (Cohen et al., 2002).

![Figure 2](https://www.aspetjournals.org/jpet/article-pdf/597/4/880/799729/jpet00004-i1665.pdf)

**Fig. 2.** SR141716 administration blocks nicotine-induced CPP. A, to induce CPP, a box with two discrete chambers, or environments, is used. Rats are repeatedly injected with nicotine before being placed in one environment and with saline before being placed in the other environment. Then, in a nicotine-free state, the animals are allowed access to both environments, and the amount of time spent in each environment is recorded. Adapted from Cami and Farre (2003). B, nicotine is able to induce significant conditioned place preferences over a large range of doses in rats. Results are expressed as the difference in time in seconds spent in the drug-paired side between the post- and preconditioning session. *, *P < 0.05. Adapted from Le Foll and Goldberg (2004a). C, when SR141716 was administered acutely before the test session, it blocked the nicotine-induced conditioned place preference without interfering with the rat’s locomotor activity. From Le Foll and Goldberg (2004b).
In human smokers, preliminary data from the STRATUS-US trial (smoking cessation in smokers motivated to quit) on the effects of SR141716 are promising (Anthenelli and Despres, 2004). This clinical study enrolled 787 smokers in 11 clinical trial sites in the United States. The participants were randomized to Rimonabant at a dose of 5 mg (n = 262) or 20 mg (n = 261) or a placebo. The study lasted 10 weeks, and the smokers were permitted to smoke during the first 2 weeks but were asked to abstain from smoking after this period. The quit rates for subjects in the 20-mg Rimonabant group were double that of the placebo group, and they showed a marked reduction in weight gain over the 10-week treatment (Anthenelli and Despres, 2004).

**Neurobiological Pathways Affected by CB₁ Blockade**

The mechanisms underlying the effects of CB₁ blockade on drug-induced reinforcement/reward and relapse to drug-seeking behavior remain unknown. Interestingly, SR141716 has been reported to block dopamine elevations in the nucleus accumbens produced by nicotine (Cohen et al., 2002) and Δ⁹-THC (Tanda et al., 1997), and SR141716 is effective in decreasing the intravenous self-administration of these two drugs (Tanda et al., 1997; Cohen et al., 2002). In contrast, SR141716 is ineffective in blocking the dopamine-releasing effect of opiates in the nucleus accumbens (Tanda and Di Chiara, 1997) and is also ineffective in blocking opiate self-administration when the opiate is continuously available under an FR1 schedule of reinforcement (De Vries et al., 2003; Solinas et al., 2003). Further studies evaluating the effects of cannabinoid CB₁ receptor blockade on the dopamine-releasing effects of ethanol and cocaine are needed to confirm the putative relation between blockade of the dopamine-releasing effect of a drug in the nucleus accumbens and blockade of its reinforcing effects with self-administration procedures.

Environmental stimuli associated with drug self-administration can also produce dopamine elevations in the nucleus accumbens (Ito et al., 2000), and it is possible that SR141716 would also block such conditioned elevations in dopamine levels, which could result in a decreased efficacy of drug-paired stimuli and therefore reduce the tendency to relapse (De Vries et al., 2001, 2003; Cohen et al., 2004; Le Foll and Goldberg, 2004b). It is also likely that drug-priming effects that lead to relapse to drug-seeking behavior may be mediated through elevation of dopamine levels (Phillips et al., 2003). Further studies are needed to confirm the role of blockade of dopamine transmission in the behavioral effects of SR141716.

It is interesting to note that a profile similar to that described above with cannabinoid CB₁ receptor antagonists has been described with dopamine D₃ receptor ligands, which also reduce drug-seeking behavior induced by drug-associated stimuli (Pilla et al., 1999; Di Ciano et al., 2003) and block drug-induced conditioning processes (Le Foll et al., 2000, 2002, 2003a,b, 2004b; Vorel et al., 2002; Francès et al., 2004) but do not alter cocaine self-administration at a low fixed ratio value (Pilla et al., 1999). Some effects of SR141716 are diminished in dopamine D₃ receptor-deficient mice (Duarte et al., 2003), suggesting that dopamine D₃ receptors are involved in CB₁ receptor-mediated processes. Since dopamine D₃ receptors and cannabinoid CB₁ receptors are both expressed in the mesolimbic dopamine brain reward circuit (Mailleux and Vanderhaeghen, 1992; Diaz et al., 2000; Le Foll et al., 2002, 2003a,b), these two types of receptors may control the dopamine-releasing effect of drug-associated cues. These effects are probably mediated through the ventral tegmental area, the nucleus accumbens, or the amygdala (Le Foll et al., 2002, 2004a). An increase of monoaminergic neurotransmission in the medial prefrontal cortex may also be implicated in these behavioral effects (Lacroix et al., 2003; Tzavara et al., 2003).

Since cannabinoid CB₁ receptors are widely expressed throughout the brain, it seems likely that several different neurotransmitter systems are affected by cannabinoid CB₁ receptor blockade (Howlett et al., 2002). For example, CB₁ receptors are expressed in areas of the hypothalamus known to regulate appetite (Schwartz et al., 2000; Cota et al., 2003). Blockade of cannabinoid CB₁ receptors seems to decrease appetite and food intake, and CB₁ receptor antagonists are promising new medications for obesity (Black, 2004). Furthermore, blockade of cannabinoid CB₁ receptors by SR141716 prevents the development of food-induced CPP (Chaperon et al., 1998). Nevertheless, the neurobiological mechanisms underlying these effects are still unclear and may also involve dopaminergic transmission (Duarte et al., 2003). Further work is needed to determine whether similar or different neurotransmitter systems are involved in the effects of cannabinoid CB₁ receptor blockade on appetite and drug-seeking behavior.

**Cannabinoid CB₁ Receptor Blockade: A Step Forward in Drug-Dependence Therapy?**

Despite advances in the understanding of neurobiological and behavioral mechanisms that lead to drug dependence over the last 20 years, no effective treatment is yet available for cocaine or Δ⁹-THC dependence. Moreover, medications available for ethanol, nicotine, or opioid dependence are ineffective in many subjects. For example, the rate of smoking cessation by subjects entering into clinical trials that combine effective medication and behavioral and cognitive therapy is around 30% at one year; most subjects relapse (Fiore, 2000). Cannabinoid CB₁ receptor antagonists represent a potentially useful tool not only for blocking the direct reinforcing effects of Δ⁹-THC, nicotine, and ethanol, but also for preventing relapse to the use of various drugs of abuse, including cocaine, methamphetamine, and heroin. In addition, environmental stimuli seem to be one of the major factors that can trigger relapse to drug use in abstinent drug abusers. This process is not only critical for psychostimulant abuse, but also for nicotine and heroin abuse (Wikler, 1973; Childress et al., 1992; O’Brien et al., 1992, 1998), and probably for other drugs of abuse such as ethanol. By reducing the motivational effects of drug-related environmental stimuli, cannabinoid CB₁ receptor antagonists might, therefore, provide an effective means for preventing relapse to drug-seeking behavior in abstinent drug abusers, providing a promising new tool for the treatment of dependence on a wide range of abused drugs.

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References


Le Foll B, Sokoloff P, Stark H, and Goldberg SR (2004b) Dopamine D3 ligands block nicotine-induced conditioned place preferences through a mechanism that does not involve discriminative-stimulus or antidepressant-like effects. Neuropharmacology, in press.


