Published in final edited form as:
Pharmacol Res. 2007 November ; 56(5): 406–417.

Modulation Of The Endo-Cannabinoid System: Therapeutic Potential Against Cocaine Dependence

Gianluigi Tanda
Psychobiology Section, Medications Discovery Research Branch, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, 5500 Nathan Shock Drive, Baltimore, MD 21224 USA

Abstract

Dependence on cocaine is still a main unresolved medical and social concern, and in spite of research efforts, no pharmacological therapy against cocaine dependence is yet available. Recent studies have shown that the endocannabinoid system participates in specific stages and aspects of drug dependence in general, and some of this evidence suggests an involvement of the cannabinoid system in cocaine effects. For example, cocaine administration has been shown to alter brain endocannabinoid levels, and the endocannabinoid system has been involved in long-term modifications of brain processes that might play a role in neuro/behavioral effects of psychostimulant drugs like cocaine. Human studies show that marijuana dependence is frequently associated with cocaine dependence, and that the cannabinoid receptor CNR1 gene polymorphism might be related to cocaine addiction. This article will review the main papers in the field showing how a modulation of different components of the cannabinoid system might interact with some of the neurobiological/behavioral effects of cocaine related to its reinforcing effects, evaluated in preclinical models or in clinical settings. The goal of this review will be to provide insights into the complex picture of cocaine abuse and addiction, and to extrapolate from such endocannabinoid-cocaine interactions useful information to test the therapeutic potential of cannabinoid ligands and endocannabinoid-level enhancers against cocaine dependence for future preclinical/clinical trials.

Keywords

cannabinoids; cocaine; addiction; behavior

1. INTRODUCTION

A number of studies suggest that the cannabinoid system interacts with cocaine's effects at different levels in the brain. For example, both CB1 agonists and cocaine selectively increase dopamine neurotransmission in the nucleus accumbens shell (1,2,3,4), a brain area believed to play a pivotal role in the addictive effects of drugs (5). It is also interesting to note that cocaine administration results in increased levels of anandamide, one of the endogenous ligands for cannabinoid receptors in the brain (6,7), and that blockade of CB1 cannabinoid receptors attenuates a dopamine signal triggered by cocaine in the NAc (8).

Send Correspondence to: Dr Gianluigi Tanda, PhD, Psychobiology Section, MDRB, NIDA/NIH/DHHS. Bldg C Room 321, 5500 Nathan Shock Drive, Baltimore, MD, 21224, USA, Tel.: 001-410-550-1737, FAX: 001-410-550-1648, E-mail: gtanda@intra.nida.nih.gov.

The cannabinoid system has also been implicated in brain processes related to potentiation or depression of the strength of synaptic signals (9,10,11,12). These so-called processes of long term potentiation and long-term depression activated by cannabinoid neurotransmission might play a significant role in those neurobiological adaptations which are believed to take an important part in the road leading from drug use to drug abuse and addiction (13,14,15). Moreover, cannabinoid receptors are located in brain areas that have been assigned a key role in brain functions linked to the development of drug-dependence (16). Plant-derived and endogenous cannabinoid ligands have been suggested to affect neurotransmitter transporter functions (17,18,19,20,21,22), which are also pharmacological targets for cocaine (23,24). Finally, it is interesting to note that cocaine dependence is often diagnosed in the presence of other drug dependencies (25), and marijuana dependence is second only to alcohol dependence as the most frequent comorbid dependence in cocaine addicts (25,26).

1.1 Overview on cocaine abuse and addiction

Cocaine abuse and addiction are widespread throughout the world, and these phenomena are driven by the ability of this drug to produce reinforcing effects by interacting with specific sites in the central nervous system (23). Cocaine binds to specific transport sites on the cell membranes of neurons that release dopamine, serotonin or noradrenaline. These transport sites have the physiological function of removing neurotransmitters from the extracellular space after their release from nerve terminals (24). Binding of cocaine to the neurotransmitters' transport sites results in blockade of the transport, increased availability of neurotransmitters for binding to their respective receptors, and ultimately increased neurotransmission (23,27).

Although cocaine also binds and blocks the transporters for serotonin and noradrenaline (24), blockade of the dopamine transporter (DAT) appears to be the pharmacological target of cocaine mainly related to its reinforcing and other behavioral effects (23,27). Thus, increased availability of dopamine for dopamine receptors is believed to mediate most of the reinforcing actions of cocaine, leading to its abuse liability (1,3,23,27). However, cocaine abuse and addiction are processes that go well beyond the pharmacological effects of cocaine on dopamine neurotransmission, so that many other factors, genetic and environmental for example, have been suggested to play a role in the complex of actions that lead from cocaine use to its abuse and addiction (28,29,30,31).

There is no specific pharmacological therapy available against cocaine's addictive effects, but researchers in the last decades have made progresses in the understanding of the neurobiology underlying cocaine's actions (29,30). Today, different aspects of cocaine abuse and addiction in humans can be modeled and studied in experimental animals. These animal models have provided valuable results leading to a better understanding of the different factors contributing to cocaine effects (32). Moreover, the models have been invaluable in the study of newly synthesized compounds acting over different neuronal systems that might become candidates for development as cocaine abuse medication (29,30).

1.2 Overview on the brain endocannabinoid system

The important discoveries in the last two decades in the cannabinoid field have provided useful information about the physiological functions of the endocannabinoid system in the brain and periphery, and the involvement of this system in the etiology and therapy of many human diseases (33,34,35). During the last decade researchers have provided evidence for the existence of at least two cannabinoid receptors, CB1 and CB2 (36,37,38,39) and we have now available different selective synthetic agonists and antagonists for both CB1 and CB2 receptors (40,41), other than classic, plant-derived cannabinoid agonists like delta-9-THC, the active ingredient in marijuana. Although the existence of novel cannabinoid receptors has been

suggested in different studies (42,43,44), definitive proof of the existence of these cannabinoid receptors has yet to be shown.

Several different endogenous ligands for CB1 and CB2 receptors have been found, such as anandamide, 2AG, noladin-ether (45,46,47,48). At variance with classical neurotransmitters, these endocannabinoids are not stored in vesicles in nerve endings, but are released “on demand” by specific changes occurring in neurons which promote the function of specific enzymes that produce anandamide or 2-AG from membrane-constituent lipids (49,50,51,52). We now have evidence that endogenous cannabinoids released “on demand” can function as retrograde messengers in the synapse (53). Thus, activation of cannabinoid receptors might change the electric equilibrium of the post-synaptic membranes with important modifications for cell-depolarization, neuronal firing, and release of classic neurotransmitters, which ultimately results in a modification of brain neurotransmission (10,11).

Some of the neurobiological effects of endocannabinoids have been demonstrated to be long-lasting, leading to the so-called processes of long-term potentiation and long-term depression of the synaptic transmission strength (11,12). It is interesting to note that these long-term effects are in spite of the very brief half life of endogenous cannabinoid ligands in the extracellular space (49,54,55).

Anandamide and 2-AG are taken-up into the cell by a not completely defined and still debated mechanism/s: passive diffusion or facilitated transport across the plasma membrane (55,56, 57,58,59). Anandamide is then metabolized into the cell by an intracellular enzyme, the fatty acid amide hydrolase (FAAH) (60,61), the blockade of which has been shown to prolong the behavioral/neurobiological effects of anandamide (4,61,62,63). In contrast, 2-AG is metabolized through the mono glyceril lipase enzyme (54). In the last few years several pharmacological tools have been discovered that alter the physiological equilibrium of the endocannabinoid system by acting on the metabolic pathways of the endogenous ligands. The result of this modulation is that blockade of endocannabinoid metabolism increases levels of endocannabinoids in specific brain areas in which there is a preexisting cannabinoid tone or where endogenous cannabinoids are released on demand triggered by specific neuronal signals (34,61). These highly-specific effects contrast with the effects of exogenously administered cannabinoid agonists, which diffuse widely throughout the brain leading to a generalized and contemporaneous activation of multiple brain areas.

It is believed that in humans, cannabinoid receptor agonists, like delta-9-THC, activate cannabinoid CB1 receptors, producing reinforcing effects which are the basis for marijuana abuse (2,64). CB1 receptors are also involved in other brain mechanisms and functions associated with pathologies in which a cannabinoid intervention might have a therapeutic value (33,34,65,66). Unfortunately, there is no cannabinoid agonist drug available yet that can selectively produce therapeutic effects without having undesired psychotropic, reinforcement-related effects. However, pharmacological tools are now available that can modulate the activity of endogenous cannabinoid ligands in selected brain areas, thereby having therapeutic value (34) without the harmful reinforcing effects produced by delta-9-THC-like drugs with the widespread action. Indeed, interesting actions of such cannabinoid modulators have been already described in preclinical models of anxiety (61,67) and depression (68), and preclinical tests so far have also shown negative results in procedures involving models of drug abuse (4,68,69).

2. Effects of cannabinoid drugs or endocannabinoid modulators in preclinical models of cocaine's behavioral and reinforcing effects

2.1 Cannabinoid interactions with cocaine-induced stimulation of motor activity and behavioral sensitization

2.1.1 Effects after acute administration of cocaine—Psychostimulants, like cocaine, have the ability to influence neuronal activity, which results in stimulation of behavioral activity. Stimulation of locomotor activity induced by cocaine and other psychostimulants has been extensively studied (see, for example citations 70, and 71). Administration of psychostimulants in rodents induces a dose-dependent increase in behavioral activation, which depends on the activation of selected brain striatal areas (72,73,74,75,76), and that is accompanied by stimulation of DA neurotransmission (3,77,78,79). Although this behavior is not a direct correlate of the reinforcing effects of cocaine, the fact that it can be obtained by injecting cocaine in the NAc (72,76,77), and that NAc DA transmission is involved in different aspects of drug abuse and addiction (5,80,81), makes monitoring of locomotor activation an easy preclinical target to test drugs that can interfere with the ability of cocaine to stimulate DA neurotransmission and potentially attenuate cocaine-induced reinforcement (82).

Do cannabinoids alter the acute effects of cocaine on stimulation of motor activities? Pryor and colleagues, 1978 (83), described the interaction between cocaine and delta-9-THC on motor activity, measured as photo-beam interruptions in rats, as one of mutual antagonism dependent on the combination of doses tested. The antagonism was attenuated but still evident after sub-chronic administration of delta-9-THC. In agreement with these data, Ferrari et al., 1999 (84), showed that HU210, a synthetic agonist for CB1 receptors, dose dependently reduced the locomotor activity induced by cocaine, 15 mg/kg i.p. in rats. However, sub-chronic administration of HU210 was not able to modify cocaine-induced locomotion at variance with the previous report. It should be noted that a cannabinoid antagonist was not available in 1978, and that Ferrari et al., 1999 (84), did not test whether a CB1 receptor antagonist could interfere with HU210 actions on cocaine effects. Because of the lack of direct pharmacological involvement of CB1 receptors in cocaine effects, Przegalinski et al., 2005 (85), tried to address this issue in a more recent report. In that study the authors showed that the CB1 receptor agonist WIN 55,212-2, but not its less active enantiomer WIN 55,212-3, dose dependently (3–6 mg/kg i.p.) reduced cocaine-induced hyper-locomotion, without affecting behavior when administered alone. Rimonabant (SR 141716), a selective antagonist of CB1 receptors (86), did not reverse the effects of WIN 55,212-2 on cocaine-stimulated locomotion, suggesting a non-CB1 mediated mechanism of action for WIN 55,212-2. Moreover, the effect was not attributable to unspecific interactions of the highly lipophilic cannabinoid agonist WIN 55,212-2 with hydrophobic sites of proteins or other cell's membrane lipid constituents, since the less active enantiomer did not show any significant effect on cocaine-induced hyper-locomotion (85). Further, the authors showed that the effects of WIN 55,212-2 resembled those of a serotonin $5HT_3$ antagonist, based on other previously published evidence (87,88), thus indicating the possibility of an involvement of $5HT_3$ receptors in the action of cannabinoid agonists on cocaine-induced hyper-locomotion. However, other than a resemblance of effects, there was no direct pharmacological evidence for $5HT_3$-receptor involvement in the actions of WIN 55,212-2 on cocaine-induce hyper-locomotion (85). It should also be noted that in the report by Przegalinski et al., 2005 (85), the locomotor stimulant effects of cocaine were reduced to a certain extent, though not significantly, by Rimonabant itself, while in a recent report (8) Rimonabant significantly attenuated cocaine-induced hyperactivity, thus suggesting the possibility that both agonist and antagonists of CB1 receptors can negatively modulate the locomotor stimulant effects of cocaine. Also, Rimonabant antagonized cocaine-induced hyper-locomotion in Gerbils habituated to the test cage, but not in non-habituated animals (89). The authors explained their results in terms of a cannabinoid involvement as a permissive element

required in the ability of cocaine to override novelty-stimulus satiation in habituated Gerbils. However, lack of effects of Rimonabant on acute cocaine-induced locomotor stimulation has also been reported in habituated mice and rats (90,91).

Taken together these experiments suggest that an endocannabinoid tone might not be necessary to mediate the acute motor stimulant effects of cocaine in rodents. However, depending on dose, both cannabinoid CB1 receptor agonists and antagonists might modulate this behavioral stimulation induced by cocaine. Moreover, as shown by Cheer et al., 2007 (8), attenuation of cocaine-induced locomotor activity by a CB1 receptor antagonist has a neurochemical correlate. In that study, Rimonabant pretreatment attenuated dopamine neurotransmission, as measured by “fast-scan-cyclic voltammetry”, suggesting that a cannabinoid tone might be involved in both neurochemical and behavioral processes triggered by cocaine (8).

2.1.2. Effects in cocaine-sensitized animals—Psychostimulant sensitization is a phenomenon that has been extensively described in rodents. It appears as an increased effectiveness of the psychostimulant drugs to produce behavioral activation in animals previously exposed to single (92) or repeated (93) administration of the same drug. Cross sensitization between different drugs has also been described (94,95).

It has been suggested that sensitization induced by drugs of abuse may be due to neuronal adaptations that play a role in the development of addictive behaviors. Behavioral sensitization is easily demonstrated in animals, and it has been hypothesized that this adaptation is involved in the transition from drug use to abuse and addiction (see citations 14, and 15, for review). Thus, behavioral sensitization has been the target of different studies searching for drugs able to impair or reduce the effects of this adaptation induced by sub-chronic/chronic administration of cocaine.

Do cannabinoids play a role in the behavioral sensitization induced by cocaine? There are only a few reports about cannabinoid interactions with development or expression of cocaine-induced behavioral sensitization. Sensitization and cross sensitization have both been reported for cannabinoid agonists and some drugs abused by humans including psychostimulant drugs (94,95,96,97,98,99,100). However, failure to develop cross sensitization in rats chronically treated with a cannabinoid agonist, CP 55,940, and challenged with cocaine has also been reported (101). In the same study, CP 55,940 failed to enhance the sensitivity to cocaine when the drugs were concurrently administered during the development phase. Also, the development of cocaine sensitization did not appear to be under control of CB1 receptors in rodents in another report (90). In this latter study, mice were treated with 20 mg/kg cocaine for 11 days in their home cages. Three days after the last cocaine injection they habituated to an open field, and then tested with cocaine (10 mg/kg). The authors reported a first set of experiments in which Rimonabant 1 mg/kg administered 30 min before the daily cocaine injection significantly reduced the locomotor sensitization induced by cocaine. Such effects, however, were not replicated in a subsequent set of experiments with increasing doses of cocaine (90).

In genetically modified CB1 receptor knock out mice (102), cocaine (10 mg/kg twice daily for 15 days) induced a behavioral sensitization, tested after one week withdrawal in an open field, which was indistinguishable from that induced in wild-type littermate control mice. These findings once more suggest a lack of involvement of the endocannabinoid system in the development of behavioral sensitization induced by cocaine. On the other hand, the expression of cocaine sensitization has been demonstrated to be impaired by cannabinoid CB1 receptor blockade, as shown by administration of the selective CB1 receptor antagonist Rimonabant together with cocaine five days after withdrawal from cocaine (103). Although this interaction needs to be further investigated, results from the cited reports suggest that even if activation

of cannabinoid neurotransmission through CB1 receptors might not be required for development of cocaine-induced sensitization, an endogenous cannabinoid tone might be essential for its expression.

Thus, cannabinoid antagonists might decrease the impact of a "sensitized" response to drug stimuli in subjects during abstinence. This prediction matches the results obtained by DeVries et al., 2001 (104), with administration of the cannabinoid receptor antagonist Rimonabant in cocaine abstinent rats during self-administration reinstatement tests (see below the section: "Effects of cannabinoids on animal models of extinction and reinstatement of cocaine-seeking behavior").

2.2 Cannabinoid interactions with cocaine-induced place conditioning

The place conditioning procedure is a model of drug reinforcement and is based on an individual's behavioral choice after a certain number of pairings of drug with one environment and placebo with another. This procedure, though simple, can give an indication of the pleasurable (place preference) or aversive (place avoidance) feelings/perceptions induced by drugs during the conditioning procedure. The place-conditioning allows the study of both development and expression of aversion or preference for a place associated with a certain drug dose (see citations 105, and 106 for review), with the final test performed with animals in a drug-free state. So, the ability of drugs to interfere or impair the effects of the conditioning-drug could be related to a potential therapeutic value, in terms of ability to reduce or block the pleasurable feelings induced by the conditioning drug, or to attenuate the strength of the association between the conditioning drug and the environmental stimuli.

It has been repeatedly shown that cocaine, just like many other drugs abused by humans, supports place preference at certain doses (106). On the other hand, results from place conditioning studies with cannabinoid agonists and antagonists have been inconsistent (see citation 107 for review), and both preference and aversion induced by cannabinoid CB1 receptor agonists and antagonists have been reported under a variety of different experimental conditions and dose ranges (108,109,110,111,112,113).

The involvement of the cannabinoid system in processes related to positive reinforcement induced by cocaine in the place conditioning procedure was evaluated by Chaperon et al., 1998 (91), in rats. The authors showed clear evidence that blockade of CB1 receptors by administration of the selective cannabinoid CB1 receptor antagonist Rimonabant impaired the acquisition of cocaine-conditioned place preference, suggesting that the development of such conditioning was under control of a cannabinoid tone in the brain. In the same paper the authors also showed that blockade of CB1 receptors did not impair the expression of cocaine-conditioned place preference when the antagonist of CB1 receptors, Rimonabant, was administered only once, 30 min before the final test, instead of 30 min before each cocaine injection during the conditioning sessions (91). At variance with this report, results from a study by Martin et al., 2000 (102), showed that development and expression of cocaine-conditioned place preference can be established in genetically modified CB1 receptor knock-out mice. These latter results suggest no involvement of the endogenous cannabinoid systems in brain processes related to the motivational effects induced by cocaine in this procedure in genetically modified mice (102). These contradictory findings (91,102) might be explained on the basis of species differences, or developmental adaptations in the regulatory processes involved in the mediation of cocaine reinforcing effects in mice genetically deficient in CB1 cannabinoid receptors. It should be noted that Rimonabant might have inverse agonist actions on CB1 receptors (114,115,116), or might possess actions over pharmacological targets other than on CB1 receptors, for example on the putative CB_3 receptor (42,65). Martin and colleagues (102) did not cite the article by Chaperon et al., 1998 (91), so we do not have their comments on this issue. We also do not have information about the effects of Rimonabant administration

on development and expression of cocaine-induced place preference in wild-type mice, an experiment that would allow a direct comparison with data obtained in CB1 KO mice (102).

2.3 Effects of cannabinoids on the discriminative stimulus effects of cocaine

The drug discrimination procedure has been extensively used in animal and human subjects to evaluate the specific perceptions/feelings produced by drug administration (117). It is likely that these subjective effects play an important role in the reinforcing effects of many drugs abused by humans. Indeed, many of these drugs produce euphoric or pleasurable sensations that are believed to be factors contributing to the abuse of substances (117).

The discriminative stimulus properties of cocaine have been evaluated in many differents studies under different conditions and in different species, including human subjects (117, 118). However, there is a very limited set of data available in which the influence of the cannabinoid system has been evaluated in animals trained to discriminate the subjective effects of cocaine from those of placebo. Delta-9-THC did not substitute for cocaine in pigeons trained to discriminate cocaine from placebo, or cocaine from morphine, suggesting that the discriminative stimulus of the cannabinoid agonist and that of cocaine do not overlap (119, 120). In a more recent report (103) the cannabinoid receptor antagonist Rimonabant did not substitute for cocaine, and did not change significantly the discriminative stimulus effects of cocaine in rats.

These limited findings indicate that the endogenous cannabinoid tone mediated by CB1 receptors does not play a role in the expression of the discriminative stimulus of cocaine. However, more detailed studies with a complete range of cannabinoid drugs (agonist, antagonist, and modulators) and doses are needed to further elucidate the role of the cannabinoid system in the subjective effects of cocaine.

2.4 Cannabinoid modulation of the effects of cocaine on thresholds for Intra Cranial Self Stimulation (ICSS)

This procedure is based on studies by Olds and Milner (121), in which rats have the opportunity to learn to repeatedly press a lever in order to obtain an electrical stimulation of the medial forebrain bundle, a component of reward circuits in the brain (122). It has been repeatedly shown that most drugs of abuse are able to lower ICSS thresholds in a dose-dependent fashion (122,123). This effect has been used as an indirect measure of their ability to produce “reward” through brain processes linked to the medial forebrain bundle. Thus, substances able to reduce or block the ability of drugs of abuse to lower the ICSS threshold may have therapeutic potential as treatments for drug abuse. While the effects of cocaine in this procedure are consistent with its reinforcing effects in animal and human subjects, inconsistent results have been obtained with administration of cannabinoid drugs (124, 125; see also citations 106, and 126, for review). There is only limited information available for combinations of cocaine and cannabinoids studied with the intracranial self stimulation procedure. In a study by Pradhan et al., 1978 (127), co-administration of delta-9-THC in rats resulted in an antagonism of the effects of cocaine, while in experiments in which delta-9-THC was administered 80 min before cocaine, the effects of cocaine were unaffected by the cannabinoid agonist. In agreement with this study, in a more recent report (128) administration of the synthetic cannabinoid agonist WIN 55,212-2 reduced the effects of cocaine on ICSS thresholds. In the same study, administration of the CB1 receptor antagonist, Rimonabant, antagonized the effects of WIN 55-212,2 on cocaine. Also, Rimonabant administration did not affect cocaine actions on this procedure, though only very low doses of the CB1 antagonist were tested (128).

These above cited reports suggest that cannabinoid agonists might have some potential activity against cocaine reinforcing effects in rodents, however, the mechanism/s for these interactions

are not clear. Drugs of abuse and intra cranial self stimulation produce reinforcing effects through the same reward circuitry (122), and also increase dopamine neurotransmission in a dopaminergic reward-related area of such circuitry (1,2,3,78,129,130) that has been related to their reinforcing effects (5,79,80). Thus, it is not apparently clear why cocaine and cannabinoid CB1 receptor agonists, which share the ability to stimulate the brain reward circuitry, may have different and antagonistic effects in this procedure. However, the fact that in rodents cannabinoid agonists do not consistently produce reinforcing effects, but do so only under certain experimental conditions (108, 124, 131, 132, 133, 134; see also 107, 126, and 135), suggests a cautious approach to the outcome of experiments involving reinforcing effects of cannabinoids in these species as compared to the well known consistent reinforcing effects of marijuana in human subjects.

2.5 Effects of cannabinoids on cocaine-maintained self-administration behavior

Although the most direct outcome of this procedure is to predict reinforcing effects and abuse liability in humans for drugs that maintain self-administration behavior in experimental animals, many other aspects of this behavioral procedure can contribute to a better understanding of the behavioral effects of drugs and drug-related cues, their related neurobiology and potential therapeutic interventions (136,137).

As a drug that is widely abused, cocaine consistently maintains intravenous self-administration behavior across a range of doses in a variety of different species (see, for example, citations 138, and 139). Although the reinforcing effects obtained by administration of plant derived cannabinoids in humans were described in books thousands of years ago, cannabinoid agonists do not consistently maintain self-administration behavior in experimental animals (see citations 107, 126, and 135 for review).

Preclinical studies have shown that pharmacological alterations of the endocannabinoid receptor system might interfere with the ability of cocaine to maintain self-administration behavior. In Long Evans rats, administration of the cannabinoid agonist WIN 55-212,2 reduced the average number of intravenous self-injections of different doses of cocaine under a fixed-ratio 1 schedule, suggesting a potentiation of cocaine effects (140). In the same report, the selective antagonist of CB1 receptors Rimonabant antagonized the effects of WIN 55-212,2 on cocaine self-administration behavior. Rimonabant, however, did not affect the behavior maintained by cocaine when administered alone (140). In agreement with this report, Rimonabant pretreatment did not show any effect on cocaine self-administration under fixed-ratio schedules of behavior in squirrel monkeys (63), an effect that has been recently replicated and confirmed (141,142). In addition, Rimonabant did not affect the number of cocaine self-injections in Wistar rats studied under a fixed-ratio 5 schedule of drug delivery (103,104). In agreement with the previous experiments in rats and primates, pre-treating C57Bl/6J mice with Rimonabant before single one-day sessions of cocaine self-administration affected neither the number of nose-pokes maintained nor the total cocaine intake during the 30-min session (90). In contrast the effects of genetic deletion of CB1 receptors have not been entirely consistent, and can differ with the effects of administering the pharmacological antagonist of CB1 receptors, Rimonabant. For example, using the single one-day cocaine self-administration procedure mutant cannabinoid CB1 receptor knock-out mice failed to self-administer morphine, but were still able to self-administer cocaine, suggesting that the endocannabinoid system was a substrate for mediating the reinforcing effects of opioids but not those of cocaine (143). At variance with these findings, a more recent report, using the same mutant cannabinoid CB1 receptor knock-out mice as subjects, showed a reduced number of mice reaching the acquisition criteria, which was also obtained within a lager number of sessions, and a significantly reduced reinforcing efficacy of cocaine (measured as the effort required to obtain a cocaine infusion) as compared to wild-type littermate control mice (144). The authors explain

their results, contrasting with those of Cossu et al., 2001 (143), in terms of different experimental conditions; freely moving mice chronically receiving cocaine self-infusions in daily sessions (144) versus mice with restrained mobility receiving cocaine during a single session (143).

Soria and colleagues (144) confirmed their data in mutant CB1 receptor knock-out mice studying the effects of pretreatments with the antagonist of CB1 receptors Rimonabant in wild-type mice on cocaine self-administration under a progressive-ratio schedule. They found that Rimonabant dose-dependently reduced the breaking point achieved by wild-type mice under the progressive-ratio schedule of cocaine self-administration, suggesting that also in normal control mice the endocannabinoid system was a substrate for the reinforcing effects of cocaine (144). It is interesting to note that in this report the authors excluded any involvement of learning/memory processes in the effects of cocaine in mice lacking the CB1 receptors because the same mice successfully acquired an operant response maintained by natural reinforcers (food and water). Also, the reduced efficacy of cocaine as a reinforcer was not the result of a diminished ability of cocaine to stimulate dopamine neurotransmission, measured by intra-cerebral microdialysis in limbic areas of mutant mice as compared to their littermate controls (144). These latter results point toward a more complicated and central involvement of the endocannabinoid system in the addictive effects of cocaine.

As neither deletion nor blockade of CB1 receptors impairs cocaine's ability to stimulate DA neurotransmission, it seems that the effects of modulation of the endocannabinoid system on cocaine self administration may be indirect. In a recent report using Sprague Dawley rats, prior exposure to delta-9-THC did not affect the acquisition and subsequent rates of cocaine self-administration under a fixed-ratio 1 schedule of injection, but did reduce the number of "cocaine-seeking" responses under a progressive-ratio schedule (145). Thus the sensitivity to delta-9-THC exposure may vary with behavioral procedure. Indeed, it has been already reported that changes in reinforcing efficacy of cocaine are hard to detect using fixed-ratio schedules of cocaine self-administration (146). In the report by Panlilio and colleagues (145), delta-9-THC pre-exposure also decreased both the number of entries in the center-zone of an open-field arena, and the time spent in the lighted compartment of the dark-light box (two different predictors of an anxiety response) in cocaine-treated rats. The authors suggested that the reduced effectiveness of cocaine as a reinforcer after delta-9-THC pre-exposure may be because the previous exposure to the cannabinoid agonist enhanced the aversive/anxiogenic effects of cocaine (145).

The contrasting results between species and schedules of drug delivery together suggest that the endocannabinoid system might impair other brain processes related to cocaine self administration which might in turn reduce the ability to detect the reinforcing effects of cocaine. Certainly, a better understanding and clinical prediction of the influence of the endocannabinoid system on the reinforcing effects of cocaine will come from studies of the effects of cannabinoid agonists and antagonists under a variety of procedures (including progressive-ratio schedules) and with a variety of cannabinoid exposure procedures in primates.

2.6 Effects of cannabinoids on animal models of extinction and reinstatement of cocaine-seeking behavior

One of the major obstacles to successfully achieving withdrawal or abstinence from drug use stems from the difficulty of finding effective strategies against relapse to drug use that is thought to result from craving for the abused substance. Other than behavioral therapy, potential pharmacological support might alleviate craving in abstinent individuals, thus reducing the likelihood of relapse. Although the validity of preclinical models of relapse to drug-seeking and drug-taking behaviors is still under discussion (147,148,149,150), these

procedures might give some useful information about which drugs and which brain areas might interfere with the processes that underlie relapse.

In the last years, as it has become increasingly clear that the endocannabinoid system plays a role in different aspects related to substance abuse, researchers have explored the involvement of the cannabinoid system in the neurobiology of relapse to drug-seeking (see citation 151 for review). In rats, when cocaine self-administration behavior was extinguished by substituting saline for cocaine injections (152), experimenter administration of increasing doses of delta-9-THC, 3 hours after withdrawal, failed to induce/reinstate cocaine-seeking behavior. However, administration of HU210, a synthetic cannabinoid agonist which has a higher affinity and greater intrinsic activity than delta-9-THC at CB1 receptors, provoked relapse to cocaine-seeking after a prolonged (14 days) withdrawal from cocaine (104). In addition to differences in treatment, the different outcome of these reports could be due to differences in abstinence strength, because in the first and second reports rats were abstinent from cocaine only for three hours (152) and 14 days (104), respectively. These different conditions might suggest time-related adaptations of the brain systems involved in cocaine-seeking behaviors (153), with no influence of the endocannabinoid system during the early stages of withdrawal from cocaine. On the other hand, when the selective antagonists of cannabinoid CB1 receptors Rimonabant and AM251 were administered alone they did not reinstate cocaine-seeking behavior (104, 154), but both drugs reduced or inhibited cocaine-seeking behavior evoked by priming injections of cocaine (104,154). It is also interesting to note that Rimonabant reduced cocaine seeking behavior induced by cocaine associated cues, but not stress-induced reinstatement (104), suggesting the involvement of the endocannabinoid system only in some specific processes or pathways related to cocaine-seeking behavior. To this end, it is also interesting to note that AM251 did not block the DA-stimulating effects of cocaine in the NAc, but it attenuated the effects of cocaine on glutamate levels in the NAc, which might be a better neurochemical correlate of cocaine-seeking behavior (154).

3. Human studies

Though not overlapping with the purpose of this review, the “gateway drug” hypothesis of marijuana use is an interesting example of a link or association between cocaine dependence and cannabinoid agonists. Following this hypothesis, marijuana consumption could serve as a gateway drug for subsequent use and abuse of other illicit substances in a progression that can lead towards dependence on heroin, cocaine or other psychostimulants (155,156,157,158). There is still an ample debate about the factors studied and taken into consideration, and the data obtained which support this theory (see for example citations 159, and 160). It is interesting to note, however, that independently from the factor/s that link marijuana use to subsequent abuse of other illegal substances, there are also studies that show a very high prevalence of marijuana use and dependence in cocaine dependent individuals (26,161,162,163). Comorbidity of cocaine dependence with other drug dependencies is also very common (25). Thus the occurrence of cannabis dependence in cocaine dependent subjects might suggest that individual vulnerability for a certain drug can be extended to other drugs (160), but also that common risk factors (genetic, environmental, etc.) might jointly influence the individual drug liability and the links between cannabis and other drug dependencies (163).

With regard to genetic risk factors, it is interesting to note that a human genetic variant of the cannabinoid receptor gene CNR1 has been associated with susceptibility of drug dependence in a non-Hispanic, Caucasian population (164). The association was stronger with intravenous drug use, and was greatest for cocaine, amphetamine, and marijuana dependence. Non-significant association data have been instead obtained in replication of the original findings by Comings and colleagues (165,166). In a recent paper (31) these contrasting data are discussed as the result of the poor definition of the cannabinoid receptor CNR1 gene’s structure,

regulation and variation. In the same report, indeed, the authors have shown an improved definition of the human cannabinoid receptor CNR1 gene's locus and variants (31), and it has been also shown that haplotypes toward the 5' end of the cannabinoid receptor CNR1 gene's exons and introns differentiate between non-drug users and drug-abusers of European-American, African-American, and Japanese subjects. Also, a recent report by Ballon and colleagues, 2006 (167), supports the association of the cannabinoid receptor CNR1 gene polymorphism with predisposition to cocaine dependence in an African-Caribbean population.

Another interesting association, from a therapeutic perspective, has been evaluated studying the relationship between marijuana use during cocaine abstinence and relapse to cocaine use. In a study by Labigalini et al., 1999 (168), the authors describe a clinical observation based on spontaneous accounts by Brazilian cocaine-crack abusers, undergoing their first psychiatric assessment, reporting use of cannabis in order to get relief from cocaine-withdrawal symptoms. From a sample of 25 subjects, 68 percent ceased to use crack-cocaine during the study, which lasted 9 months. The small sample and the short period of time suggest a cautious approach to the results outcome; further studies are warranted. A more recent study (169) in New York used a much larger sample of cocaine addicts (144 subjects), and examined whether cannabis use after discharge from inpatient treatment could affect relapse to cocaine use. Data from this study showed that about a third of the subjects used cannabis after discharge and that cannabis use substantially increased the risk of relapse to cocaine use, significantly reduced the achievement of sustained remission, and significantly increased relapse to cocaine use after sustained remission (169). In agreement with this latter report is a preclinical investigation (described above, section 2.6) showing cannabinoid-induced reinstatement of cocaine seeking behavior in rodents (104).

4. Summary and concluding remarks

Most of the scientific articles reviewed in the present manuscript have described studies of cannabinoid CB1 receptor agonists and antagonists tested against cocaine effects in preclinical models thought to be predictive of cocaine abuse. These studies have provided interesting results, especially for the ability of cannabinoid antagonists, and Rimonabant in particular, to significantly counteract some of the reinforcing actions of cocaine (104,143). Collectively, the studies suggest that a cannabinoid tone, impaired by cannabinoid antagonist administration, is indeed involved in many of the reinforcing effects of cocaine which are believed to be responsible for cocaine abuse and addiction. On the other hand, there are no studies available showing interactions of drugs acting as cannabinoid levels modulators/enhancers on cocaine-induced behaviors. These drugs affecting directly the endogenous cannabinoid tone could interfere with cocaine effects in these preclinical procedures and could substantially increase our knowledge about the cannabinoid-neurobiology related to cocaine dependence.

Suggestions about possible genetic predisposition/vulnerability to cocaine dependence from human studies due to variants of the cannabinoid receptor CNR1 gene have given more strength to the link between endocannabinoids and cocaine. Due to the widespread distribution of cannabinoid receptors in the brain, and their abundance in brain areas playing pivotal roles in drug abuse and addiction, the different expression and regulation of cannabinoid receptors induced by genetic differences (31) might be an important factor in the predisposition or vulnerability to drug dependence. For this reason, the potential to directly interact with endocannabinoid tone in selected brain areas, an effect that can be obtained with endocannabinoid uptake inhibitors or metabolism blockers (4,60,62)(as shown also in genetically modified mice, 170), as compared to widespread actions of cannabinoid receptors agonists/antagonists, should be one of the next challenges in the research for medications able to counteract the abuse- and dependence-related behavioral/neurobiological effects of cocaine.

Acknowledgements

The author acknowledges the helpful comments and suggestions of Dr. Jonathan L. Katz, Dr. Sergi Ferré, Dr. Leigh V. Panlilio and Dr. M. Scherma.

This research was supported by the Intramural Research Program of the NIH, National Institute on Drug Abuse.

References

1. Pontieri FE, Tanda G, Di Chiara G. Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the “shell” as compared with the “core” of the rat nucleus accumbens. Proc Natl Acad Sci USA 1995;92:12304–8. [PubMed: 8618890]
2. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. Science 1997;276:2048–50. [PubMed: 9197269]
3. Tanda G, Pontieri FE, Frau R, Di Chiara G. Contribution of blockade of the noradrenaline carrier to the increase of extracellular dopamine in the rat prefrontal cortex by amphetamine and cocaine. Eur J Neurosci 1997;9(10):2077–85. [PubMed: 9421168]
4. Solinas M, Justinova Z, Goldberg SR, Tanda G. Anandamide administration alone and after inhibition of fatty acid amide hydrolase (FAAH) increases dopamine levels in the nucleus accumbens shell in rats. J Neurochem 2006;98(2):408–19. [PubMed: 16805835]
5. Di Chiara G, Tanda G, Bassareo V, Pontieri F, Acquas E, Fenu S, Cadoni C, Carboni E. Drug addiction as a disorder of associative learning. Role of nucleus accumbens shell/extended amygdala dopamine. Ann NY Acad Sci 1999;877:461–85. [PubMed: 10415665]
6. Gonzalez S, Cascio MG, Fernandez-Ruiz J, Fezza F, Di Marzo V, Ramos JA. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res 2002;954(1):73–81. [PubMed: 12393235]
7. Gonzalez S, Fernandez-Ruiz J, Sparpaglione V, Parolaro D, Ramos JA. Chronic exposure to morphine, cocaine or ethanol in rats produced different effects in brain cannabinoid CB(1) receptor binding and mRNA levels. Drug Alcohol Depend 2002;66(1):77–84. [PubMed: 11850139]
8. Cheer JF, Wassum KM, Sombers LA, Heien ML, Ariansen JL, Aragona BJ, Phillips PE, Wightman RM. Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J Neurosci 2007;27(4):791–5. [PubMed: 17251418]
9. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science 2002;296:678–82. [PubMed: 11976437]
10. Huang YC, Wang SJ, Chiou LC, Gean PW. Mediation of amphetamine-induced long-term depression of synaptic transmission by CB1 cannabinoid receptors in the rat amygdala. J Neurosci 2003;23(32): 10311–20. [PubMed: 14614090]
11. Robbe D, Kopf M, Remaury A, Bockaert J, Manzoni OJ. Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. Proc Natl Acad Sci USA 2002;99(12):8384–8. [PubMed: 12060781]
12. Robbe D, Alonso G, Manzoni OJ. Exogenous and endogenous cannabinoids control synaptic transmission in mice nucleus accumbens. Ann N Y Acad Sci 2003;1003:212–25. [PubMed: 14684448]
13. Thomas MJ, Beurrier C, Bonci A, Malenka RC. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. Nat Neurosci 2001;4(12):1217–23. [PubMed: 11694884]
14. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 1993;18(3):247–291. [PubMed: 8401595]
15. Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction 2001;96:103–14. [PubMed: 11177523]
16. Mailleux P, Vanderhaeghen JJ. Distribution of the neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and in situ hybridization histochemistry. Neuroscience 1992;48:655–88. [PubMed: 1376455]

17. Hershkowitz M. The effect of in vivo treatment with (−) delta 1-tetrahydrocannabinol, and other psychoactive drugs on the in vitro uptake of biogenic amines. Adv Biosci 1978;22–23:351–8.
18. Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J Pharmacol Exp Ther 1975;194(1):74–81. [PubMed: 168349]
19. Johnson KM, Dewey WL, Harris LS. Some structural requirements for inhibition of high-affinity synaptosomal serotonin uptake by cannabinoids. Mol Pharmacol 1976;12(3):345–52. [PubMed: 934055]
20. Chen J, Paredes W, Li J, Smith D, Lowinson JH, Gardner EL. Δ9-Tetrahydrocannabinol produces naloxoneblockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. Psychopharmacology 1990;102:156–162. [PubMed: 2177204]
21. Chen J, Paredes W, Lowinson JH, Gardner EL. Strain-specific facilitation of dopamine efflux by 9-tetrahydrocannabinol in the nucleus accumbens of rat: An in vivo microdialysis study. Neurosci Lett 1991;129:136–140. [PubMed: 1656336]
22. Seillier, AJ.; Price, DA.; Giuffrida, A. Society for Neuroscience. Atlanta, GA: 2006. Effects of endocannabinoids on dopamine uptake in rat caudate-putamen, nucleus accumbens, and prefrontal cortex. Online Meeting Abstracts (35.3/C41)
23. Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 1987;237:1219–23. [PubMed: 2820058]
24. Ritz MC, Cone EJ, Kuhar MJ. Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure-activity study. Life Sci 1990;46(9):635–45. [PubMed: 2308472]
25. Miller NS, Summers GL, Gold MS. Cocaine dependence: alcohol and other drug dependence and withdrawal characteristics. J Addict Dis 1993;12(1):25–35. [PubMed: 8381028]
26. Miller NS, Gold MS, Belkin BM. The diagnosis of alcohol and cannabis dependence in cocaine dependence. Adv Alcohol Subst Abuse 1990;8(3–4):33–42. [PubMed: 2343796]
27. Kuhar MJ, Ritz MC, Boja JW. The dopamine hypothesis of the reinforcing properties of cocaine. Trends Neurosci 1991;14(7):299–302. [PubMed: 1719677]
28. Saxon AJ, Oreskovich MR, Brkanac Z. Genetic determinants of addiction to opioids and cocaine. Harv Rev Psychiatry 2005;13(4):218–32. [PubMed: 16126608]
29. Carroll FI, Howell LL, Kuhar MJ. Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. J Med Chem 1999;42(15):2721–36. [PubMed: 10425082]
30. Newman AH, Kulkarni S. Probes for the dopamine transporter: new leads toward a cocaine-abuse therapeutic--A focus on analogues of benztropine and rimcazole. Med Res Rev 2002;22(5):429–64. [PubMed: 12210554]
31. Zhang PW, Ishiguro H, Ohtsuki T, Hess J, Carillo F, Walther D, Onaivi ES, Arinami T, Uhl GR. Human cannabinoid receptor 1: 5' exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. Mol Psychiatry 2004;9(10):916–31. [PubMed: 15289816]
32. Sanger, DJ. Screening for abuse and dependence liabilities. In: Willner, P., editor. Behavioral Models in Psychopharmacology: Theoretical, Industrial and Clinic Perspectives. Cambridge: Cambridge University Press; 1991. p. 485-502.
33. Piomelli D, Giuffrida A, Calignano A, Rodriguez de Fonseca F. The endocannabinoid system as a target for therapeutic drugs. Trends Pharmacol Sci 2000;21(6):218–24. [PubMed: 10838609]
34. Piomelli D. The endocannabinoid system: a drug discovery perspective. Curr Opin Investig Drugs 2005;6(7):672–9.
35. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006;58(3):389–62. [PubMed: 16968947]
36. Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;34:605–13. [PubMed: 2848184]
37. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–4. [PubMed: 2165569]
38. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365(6441):61–5. [PubMed: 7689702]

39. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54(2):161–202. [PubMed: 12037135]
40. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. Int J Obes (Lond) 2006;30(Suppl 1):S13–8. [PubMed: 16570099]
41. Palmer SL, Thakur GA, Makriyannis A. Cannabinergic ligands. Chem Phys Lipids 2002;121:3–19. [PubMed: 12505686]
42. Járai Z, Wagner JA, Varga K, Lake KD, Compton DR, Martin BR, Zimmer AM, Bonner TI, Buckley NE, Mezey E, Razdan RK, Zimmer A, Kunos G. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Natl Acad Sci U S A 1999;96 (24):14136–41. [PubMed: 10570211]
43. Hajos N, Freund TF. Distinct cannabinoid sensitive receptors regulate hippocampal excitation and inhibition. Chem Phys Lipids 2002;121(1–2):73–82. [PubMed: 12505692]
44. Begg M, Pacher P, Batkai S, Osei-Hyiaman D, Offertaler L, Mo FM, Liu J, Kunos G. Evidence for novel cannabinoid receptors. Pharmacol Ther 2005;106(2):133–45. [PubMed: 15866316]
45. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946–49. [PubMed: 1470919]
46. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR, Pertwee RG, Griffin G, Bayewitch M, Barg J, Vogel Z. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995;50:83–90. [PubMed: 7605349]
47. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun 1995;215(1):89–97. [PubMed: 7575630]
48. Hanus L, Abu-Lafi S, Fride E, Breuer A, Vogel Z, Shalev DE, Kustanovich I, Mechoulam R. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proc Natl Acad Sci USA 2001;98(7):3662–5. [PubMed: 11259648]
49. Di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz JC, Piomelli D. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 1994;372:686–91. [PubMed: 7990962]
50. Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. Nature 1997;388(6644):773–8. [PubMed: 9285589]
51. Bisogno T, Sepe N, Melck D, Maurelli S, De Petrocellis L, Di Marzo V. Biosynthesis, release and degradation of the novel endogenous cannabimimetic metabolite 2-arachidonoylglycerol in mouse neuroblastoma cells. Biochem J 1997;322(Pt 2):671–7. [PubMed: 9065792]
52. Liu J, Wang L, Harvey-White J, Osei-Hyiaman D, Razdan R, Gong Q, Chan AC, Zhou Z, Huang BX, Kim HY, Kunos G. A biosynthetic pathway for anandamide. Proc Natl Acad Sci USA 2006;103 (36):13345–50. [PubMed: 16938887]
53. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 2001;410(6828):588–92. [PubMed: 11279497]
54. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, Kathuria S, Piomelli D. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci U S A 2002;99(16):10819–24. [PubMed: 12136125]
55. Ligresti A, Cascio MG, Di Marzo V. Endocannabinoid metabolic pathways and enzymes. Curr Drug Targets CNS Neurol Disord 2005;4(6):615–23. [PubMed: 16375679]
56. Hillard CJ, Jarrahian A. The movement of N-arachidonoylethanolamine (anandamide) across cellular membranes. Chem Phys Lipids 2000;108(1–2):123–34. [PubMed: 11106786]
57. Hillard CJ, Jarrahian A. Cellular accumulation of anandamide: consensus and controversy. Br J Pharmacol 2003;140(5):802–8. [PubMed: 12970089]
58. McFarland MJ, Barker EL. Anandamide transport. Pharmacol Ther 2004;104(2):117–35. [PubMed: 15518883]

59. Beltramo M, Stella N, Calignano A, Lin SY, Makriyannis A, Piomelli D. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. Science 1997;277(5329):1094–7. [PubMed: 9262477]
60. Ueda N, Kurahashi Y, Yamamoto S, Tokunaga T. Partial purification and characterization of the porcine brain enzyme hydrolyzing and synthesizing anandamide. J Biol Chem 1995;270(40):23823–7. [PubMed: 7559559]
61. Kathuria S, Gaetani S, Fegley D, Valino F, Duranti A, Tontini A, Mor M, Tarzia G, La Rana G, Calignano A, Giustino A, Tattoli M, Palmery M, Cuomo V, Piomelli D. Modulation of anxiety through blockade of anandamide hydrolysis. Nat Med 2003;9(1):76–81. [PubMed: 12461523]
62. Fegley D, Gaetani S, Duranti A, Tontini A, Mor M, Tarzia G, Piomelli D. Characterization of the fatty acid amide hydrolase inhibitor cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester (URB597): effects on anandamide and oleoylethanolamide deactivation. J Pharmacol Exp Ther 2005;313(1):352–8. [PubMed: 15579492]
63. Solinas M, Tanda G, Justinova Z, Wertheim CE, Yasar S, Piomelli D, Vadivel SK, Makriyannis A, Goldberg SR. The endogenous cannabinoid anandamide produces THC-like discriminative and neurochemical effects that are enhanced by inhibition of fatty acid amide hydrolase (FAAH) but not by inhibition of anandamide transport. J Pharmacol Exp Ther 2007;321(1):370–80. [PubMed: 17210800]
64. Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci 2000;3:1073–4. [PubMed: 11036260]
65. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83(3):1017–66. [PubMed: 12843414]
66. Porter AC, Felder CC. The endocannabinoid nervous system: unique opportunities for therapeutic intervention. Pharmacol Ther 2001;90(1):45–60. [PubMed: 11448725]
67. Braida D, Limonta V, Malabarba L, Zani A, Sala M. 5-HT1A receptors are involved in the anxiolytic effect of Delta9-tetrahydrocannabinol and AM 404, the anandamide transport inhibitor, in Sprague-Dawley rats. Eur J Pharmacol 2007;555(2–3):156–63. [PubMed: 17116299]
68. Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, Cassano T, Morgese MG, Debonnel G, Duranti A, Tontini A, Tarzia G, Mor M, Trezza V, Goldberg SR, Cuomo V, Piomelli D. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci U S A 2005;102(51):18620–5. [PubMed: 16352709]
69. Vlachou S, Nomikos GG, Panagis G. Effects of endocannabinoid neurotransmission modulators on brain stimulation reward. Psychopharmacology 2006;188(3):293–305. [PubMed: 16953388]
70. Dews PB. The measurement of the influence of drugs on voluntary activity in mice. Brit J Pharmacol 1953;8:46–8.
71. Scheel-Kruger, J.; Braestrup, C.; Mogens, N.; Golembiwska, K.; Mogilnicka, E. Cocaine: Discussion on the Role of Dopamine in the Biochemical Mechanism of Action. In: Ellinwood, EH., Jr; Kilbey, MM., editors. Cocaine and Other Stimulants. Advances in Behavioral Biology. 21. New York and London: Plenum Press; 1977. p. 373-407.
72. Kelly PH, Iversen SD. Selective 6OHDA-induced destruction of mesolimbic dopamine neurons: abolition of psychostimulant-induced locomotor activity in rats. Eur J Pharmacol 1976;40(1):45–56. [PubMed: 1033072]
73. Swanson CJ, Heath S, Stratford TR, Kelley AE. Differential behavioral responses to dopaminergic stimulation of nucleus accumbens subregions in the rat. Pharmacol Biochem Behav 1997;58(4):933–45. [PubMed: 9408198]
74. Sellings LH, Clarke PB. Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. J Neurosci 2003;23(15):6295–303. [PubMed: 12867514]
75. Sellings LH, McQuade LE, Clarke PB. Evidence for multiple sites within rat ventral striatum mediating cocaine-conditioned place preference and locomotor activation. J Pharmacol Exp Ther 2006;317(3):1178–87. [PubMed: 16507711]
76. Ikemoto S. Ventral striatal anatomy of locomotor activity induced by cocaine, D-amphetamine, dopamine and D1/D2 agonists. Neuroscience 2002;113(4):939–55. [PubMed: 12182899]

77. Tolliver BK, Newman AH, Katz JL, Ho LB, Fox LM, Hsu K Jr, Berger SP. Behavioral and neurochemical effects of the dopamine transporter ligand 4chlorobenztropine alone and in combination with cocaine in vivo. J Pharmacol Exp Ther 1999;289(1):110–22. [PubMed: 10086994]
78. Tanda G, Ebbs A, Newman AH, Katz JL. Effects of 4′-chloro-3 alpha-(diphenylmethoxy)-tropane on mesostriatal, mesocortical, and mesolimbic dopamine transmission: comparison with effects of cocaine. J Pharmacol Exp Ther 2005;313(2):613–20. [PubMed: 15681658]
79. Tanda G, Ebbs AL, Kopajtic TA, Elias LM, Campbell BL, Newman AH, Katz JL. Effects of Muscarinic M1 Receptor Blockade on Cocaine-Induced Elevations of Brain Dopamine levels and Locomotor Behavior in Rats. J Pharmacol Exp Ther 2007;321(1):334–344. [PubMed: 17255465]
80. Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. Science 1997;278:52–8. [PubMed: 9311926]
81. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostatis. Neuropsychopharmacology 2001;24:97–129. [PubMed: 11120394]
82. Desai RI, Kopajtic TA, Koffarnus M, Newman AH, Katz JL. Identification of a dopamine transporter ligand that blocks the stimulant effects of cocaine. J Neurosci 2005;25(8):1889–93. [PubMed: 15728828]
83. Pryor GT, Larsen FF, Husain S, Braude MC. Interactions of delta9-tetrahydrocannabinol with d-amphetamine, cocaine, and nicotine in rats. Pharmacol Biochem Behav 1978;8(3):295–318. [PubMed: 652837]
84. Ferrari F, Ottani A, Giuliani D. Influence of the cannabinoid agonist HU 210 on cocaine- and CQP 201-403-induced behavioural effects in rat. Life Sci 1999;65(8):823–31. [PubMed: 10466748]
85. Przegalinski E, Gothert M, Frankowska M, Filip M. WIN 55,212-2-induced reduction of cocaine hyperlocomotion: possible inhibition of 5-HT(3) receptor function. Eur J Pharmacol 2005;517(1–2): 68–73. [PubMed: 15961074]
86. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, Ferrara P, Soubrie P, Breliere JC, Le Fur GL. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994;350:240–4. [PubMed: 8070571]
87. Barann M, Molderings G, Bruss M, Bonisch H, Urban BW, Gothert M. Direct inhibition by cannabinoids of human 5-HT3A receptors: probable involvement of an allosteric modulatory site. Br J Pharmacol 2002;137(5):589–96. [PubMed: 12381672]
88. Oz M, Zhang L, Morales M. Endogenous cannabinoid, anandamide, acts as a noncompetitive inhibitor on 5HT3 receptor-mediated responses in Xenopus oocytes. Synapse 2002;46(3):150–6. [PubMed: 12325042]
89. Poncelet M, Barnouin MC, Breliere JC, Le Fur G, Soubrie P. Blockade of cannabinoid (CB1) receptors by 141716 selectively antagonizes drug-induced reinstatement of exploratory behaviour in gerbils. Psychopharmacology 1999;144(2):144–50. [PubMed: 10394995]
90. Lesscher HM, Hoogveld E, Burbach JP, van Ree JM, Gerrits MA. Endogenous cannabinoids are not involved in cocaine reinforcement and development of cocaine-induced behavioural sensitization. Eur Neuropsychopharmacol 2005;15(1):31–7. [PubMed: 15572271]
91. Chaperon F, Soubrie P, Puech AJ, Thiebot MH. Involvement of central cannabinoid (CB1) receptors in the establishment of place conditioning in rats. Psychopharmacology 1998;135:324–332. [PubMed: 9539255]
92. Ungless MA, Whistler JL, Malenka RC, Bonci A. Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. Nature 2001;411(6837):583–7. [PubMed: 11385572]
93. Martin-Iverson MT, Burger LY. Behavioral sensitization and tolerance to cocaine and the occupation of dopamine receptors by dopamine. Mol Neurobiol 1995;11(1–3):31–46. [PubMed: 8561966]
94. Pontieri FE, Monnazzi P, Scontrini A, Buttarelli FR, Patacchioli FR. Behavioral sensitization to heroin by cannabinoid pretreatment in the rat. Eur J Pharmacol 2001;421:R1–R3. [PubMed: 11516439]
95. Pontieri FE, Monnazzi P, Scontrini A, Buttarelli FR, Patacchioli FR. Behavioral sensitization to WIN55212.2 in rats pretreated with heroin. Brain Res 2001;898(1):178–80. [PubMed: 11292463]
96. Pertwee RG, Stevenson LA, Griffin G. Cross-tolerance between delta-9-tetrahydrocannabinol and the cannabimimetic agents, CP 55,940, WIN 55,212-2 and anandamide. Br J Pharmacol 1993;110:1483–90. [PubMed: 8306090]

97. Gorriti MA, Rodriguez de Fonseca F, Navarro M, Palomo T. Chronic (−)-delta9-tetrahydrocannabinol treatment induces sensitization to the psychomotor effects of amphetamine in rats. Eur J Pharmacol 1999;365(2–3):133–42. [PubMed: 9988095]

98. Muschamp JW, Siviy SM. Behavioral sensitization to amphetamine follows chronic administration of the CB1 agonist WIN 55,212-2 in Lewis rats. Pharmacol Biochem Behav 2002;73(4):835–42. [PubMed: 12213529]

99. Lamarque S, Taghzouti K, Simon H. Chronic treatment with Delta(9)-tetrahydrocannabinol enhances the locomotor response to amphetamine and heroin. Implications for vulnerability to drug addiction. Neuropharmacology 2001;41(1):118–29. [PubMed: 11445192]

100. Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G. Behavioural sensitization after repeated exposure to delta(9)-tetrahydrocannabinol and cross-sensitization with morphine. Psychopharmacology 2001;158:259–266. [PubMed: 11713615]

101. 101Arnold JC, Topple AN, Hunt GE, McGregor IS. Effects of pre-exposure and co-administration of the cannabinoid receptor agonist CP 55,940 on behavioral sensitization to cocaine. Eur J Pharmacol 1998;354(1):9–16. [PubMed: 9726625]

102. Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O. Cocaine, but not morphine, induces conditioned place preference and sensitization to locomotor responses in CB1 knockout mice. Eur J Neurosci 2000;12:4038–46. [PubMed: 11069600]

103. Filip M, Golda A, Zaniewska M, McCreary AC, Nowak E, Kolasiewicz W, Przegalinski E. Involvement of cannabinoid CB(1) receptors in drug addiction: effects of rimonabant on behavioral responses induced by cocaine. Pharmacol Rep 2006;58(6):806–19. [PubMed: 17220538]

104. De Vries TJ, Shaham Y, Homberg JR, Crombag H, Schuurman K, Dieben J, Vanderschuren LJ, Schoffelmeer AN. A cannabinoid mechanism in relapse to cocaine seeking. Nat Med 2001;7(10): 1151–4. [PubMed: 11590440]

105. Bardo MT, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology 2000;153(1):31–43. [PubMed: 11255927]

106. Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol 1998;56(6): 613–72. [PubMed: 9871940]

107. Tanda G, Goldberg SR. Cannabinoids: reward, dependence, and underlying neurochemical mechanisms—a review of recent preclinical data. Psychopharmacology 2003;169(2):115–34. [PubMed: 12827346]

108. Lepore M, Vorel SR, Lowinson J, Gardner EL. Conditioned place preference induced by Δ9-tetrahydrocannabinol: Comparison with cocaine, morphine, and food reward. Life Sci 1995;56:2073–80. [PubMed: 7776834]

109. Valjent E, Maldonado R. A behavioural model to reveal place preference to delta 9-tetrahydrocannabinol in mice. Psychopharmacology 2000;147:436–8. [PubMed: 10672638]

110. Braida D, Pozzi M, Cavallini R, Sala M. Conditioned place preference induced by the cannabinoid agonist CP 940: interaction with the opioid system. Neuroscience 2001;104(4):923–926. [PubMed: 11457579]

111. Braida D, Iosue S, Pegorini S, Sala M. Delta9-tetrahydrocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. Eur J Pharmacol 2004;506(1): 63–9. [PubMed: 15588625]

112. Ghozland S, Mathews H, Simonin F, Filliol D, Kieffer BL, Maldonado R. Motivational effects of cannabinoids are mediated by μ and κ-opioid receptors. J Neurosci 2002;22:1146–54. [PubMed: 11826143]

113. Le Foll B, Wiggins M, Goldberg SR. Nicotine pre-exposure does not potentiate the locomotor or rewarding effects of Delta-9-tetrahydrocannabinol in rats. Behav Pharmacol 2006;17(2):195–9. [PubMed: 16495727]

114. Pan X, Ikeda SR, Lewis DL. SR 141716A acts as an inverse agonist to increase neuronal voltage-dependent Ca2+ currents by reversal of tonic CB1 cannabinoid receptor activity. Mol Pharmacol 1998;54(6):1064–72. [PubMed: 9855635]

115. MacLennan SJ, Reynen PH, Kwan J, Bonhaus DW. Evidence for inverse agonism of SR141716A at human recombinant cannabinoid CB1 and CB2 receptors. Br J Pharmacol 1998;124(4):619–22. [PubMed: 9690851]
116. Landsman RS, Burkey TH, Consroe P, Roeske WR, Yamamura HI. SR141716A is an inverse agonist at the human cannabinoid CB1 receptor. Eur J Pharmacol 1997;334(1):R1–2. [PubMed: 9346339]
117. Holtzman, SG. Discriminative stimulus effects of drugs: relationship to potential for abuse. In: Adler, MW.; Cowan, A., editors. Modern methods in pharmacology, Vol 6. Testing and evaluation of drugs of abuse. New York: Wiley-Liss Inc; 1990. p. 193-210.
118. Woolverton WL. Discriminative stimulus effects of cocaine. NIDA Res Monogr 1991;116:61–74. [PubMed: 1369682]
119. Jarbe TU. Discriminative stimulus properties of cocaine. Effects of apomorphine, haloperidol, procaine and other drugs. Neuropharmacology 1984;23(8):899–907. [PubMed: 6090966]
120. Swedberg MD, Jarbe TU. Drug discrimination procedures: roles of relative stimulus control in two-drug cases. Psychopharmacology 1985;86(4):444–51. [PubMed: 3929316]
121. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 1954;47:419–27. [PubMed: 13233369]
122. Wise RA. Addictive drugs and brain stimulation reward. Annu Rev Neurosci 1996;19:319–340. [PubMed: 8833446]
123. Olds ME, Fobes JL. The central basis of motivation: intracranial self-stimulation studies. Ann Rev Psychol 1981;32:523–74. [PubMed: 7015997]
124. Lepore M, Liu X, Savage V, Matalon D, Gardner EL. Genetic differences in Δ^9-tetrahydrocannabinol-induced facilitation of brain stimulation reward as measured by a rate-frequency curve-shift electrical brain stimulation paradigm in three different rat strains. Life Sci (Pharmacol Lett) 1996;58:PL365–72.
125. Arnold JC, Hunt GE, McGregor IS. Effects of the cannabinoid receptor agonist CP 55,940 and the cannabinoid receptor antagonist SR 141716 on intracranial self-stimulation in Lewis rats. Life Sci 2001;70:97–108. [PubMed: 11764010]
126. Gardner EL, Vorel SR. Cannabinoid transmission and reward related events. Neurobiol Dis 1998;5:502–33. [PubMed: 9974181]
127. Pradhan SN, Bhattacharyya AK, Aulakh CS, Pradhan S, Bailey PT. Cannabis and brain-stimulation reward. Adv Biosci 1978;22–23:567–83.
128. Vlachou S, Nomikos GG, Panagis G. WIN 55,212–2 decreases the reinforcing actions of cocaine through CB1 cannabinoid receptor stimulation. Behav Brain Res 2003;141(2):215–22. [PubMed: 12742258]
129. Chen J, Marmur R, Pulles A, Paredes W, Gardner EL. Ventral tegmental microinjection of delta 9-tetrahydrocannabinol enhances ventral tegmental somatodendritic dopamine levels but not forebrain dopamine levels: evidence for local neural action by marijuana's psychoactive ingredient. Brain Res 1993;621(1):65–70. [PubMed: 8221074]
130. Chen N, Appell M, Berfield JL, Reith ME. Inhibition by arachidonic acid and other fatty acids of dopamine uptake at the human dopamine transporter. Eur J Pharmacol 2003;478(2–3):89–95. [PubMed: 14575792]
131. Takahashi RN, Singer G. Effects of body weight levels on cannabis self-administration. Pharmacol Biochem Behav 1980;13:877–81. [PubMed: 6259669]
132. Takahashi RN, Singer G. Cross self-administration of delta 9-tetrahydrocannabinol and D-amphetamine in rats. Braz J Med Biol Res 1981;14:395–400. [PubMed: 6153044]
133. Martellotta MC, Cossu G, Fattore L, Gessa GL, Fratta W. Self-administration of the cannabinoid receptor agonist WIN 55,212-2 in drug-naive mice. Neuroscience 1998;85:327–30. [PubMed: 9622233]
134. Fattore L, Cossu G, Martellotta CM, Fratta W. Intravenous self-administration of the cannabinoid CB1 receptor agonist WIN 55,212-2 in rats. Psychopharmacology 2001;156:410–416. [PubMed: 11498718]
135. Justinova Z, Goldberg SR, Heishman SJ, Tanda G. Self-administration of cannabinoids by experimental animals and human marijuana smokers. Pharmacol Biochem Behav 2005;81(2):285–99. [PubMed: 15932767]

136. Griffiths, RR.; Bigelow, GE.; Henningfield, JE. Similarities in animal and human drug-taking behavior. In: Mello, NK., editor. Advances in Substance Abuse. 1. Washington DC: JAI Press; 1980. p. 1-90.

137. Johanson CE, Balster RL. A summary of the results of a drug selfadministration study using substitution procedures in rhesus monkeys. Bull Narcotics 1978;30:43–54.

138. LeSage MG, Stafford D, Glowa JR. Preclinical research on cocaine self-administration: environmental determinants and their interaction with pharmacological treatment. Neurosci Biobehav Rev 1999;23(5):717–41. [PubMed: 10392662]

139. Porrino LJ, Daunais JB, Smith HR, Nader MA. The expanding effects of cocaine: studies in a nonhuman primate model of cocaine self-administration. Neurosci Biobehav Rev 2004;27(8):813–20. [PubMed: 15019430]

140. Fattore L, Martellotta MC, Cossu G, Mascia MS, Fratta W. CB1 cannabinoid receptor agonist WIN 55,212-2 decreases intravenous cocaine self-administration in rats. Behav Brain Res 1999;104(1–2):141–6. [PubMed: 11125733]

141. Justinova Z, Tanda G, Redhi GH, Goldberg SR. Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. Psychopharmacology 2003;169(2):135–40. [PubMed: 12827345]

142. Justinova Z, Solinas M, Tanda G, Redhi GH, Goldberg SR. The endogenous cannabinoid anandamide and its synthetic analog R(+)-methanandamide are intravenously self-administered by squirrel monkeys. J Neurosci 2005;25(23):5645–50. [PubMed: 15944392]

143. Cossu G, Ledent C, Fattore L, Imperato A, Bohme GA, Parmentier M, Fratta W. Cannabinoid CB1 receptor knockout mice fail to self-administer morphine but not other drugs of abuse. Behav Brain Res 2001;118(1):61–5. [PubMed: 11163634]

144. Soria G, Mendizabal V, Tourino C, Robledo P, Ledent C, Parmentier M, Maldonado R, Valverde O. Lack of CB1 cannabinoid receptor impairs cocaine self-administration. Neuropsychopharmacology 2005;30(9):1670–80. [PubMed: 15742004]

145. Panlilio LV, Solinas M, Matthews SA, Goldberg SR. Previous exposure to THC alters the reinforcing efficacy and anxiety-related effects of cocaine in rats. Neuropsychopharmacology 2007;32(3):646–57. [PubMed: 16738542]

146. Arnold JM, Roberts DC. A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement. Pharmacol Biochem Behav 1997;57(3):441–7. [PubMed: 9218268]

147. Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology 2003;168(1–2):3–20. [PubMed: 12402102]

148. Katz JL, Higgins ST. The validity of the reinstatement model of craving and relapse to drug use. Psychopharmacology 2003;168(1–2):21–30. [PubMed: 12695875]

149. Epstein DH, Preston KL. The reinstatement model and relapse prevention: a clinical perspective. Psychopharmacology 2003;168(1–2):31–41. [PubMed: 12721778]

150. Epstein DH, Preston KL, Stewart J, Shaham Y. Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. Psychopharmacology 2006;189(1):1–16. [PubMed: 17019567]

151. Fattore L, Spano MS, Deiana S, Melis V, Cossu G, Fadda P, Fratta W. An endocannabinoid mechanism in relapse to drug seeking: a review of animal studies and clinical perspectives. Brain Res Rev 2007;53(1):1–16. [PubMed: 16839608]

152. Schenk S, Partridge B. Cocaine-seeking produced by experimenter-administered drug injections: dose-effect relationships in rats. Psychopharmacology 1999;147(3):285–90. [PubMed: 10639687]

153. Grimm JW, Hope BT, Wise RA, Shaham Y. Neuroadaptation. Incubation of cocaine craving after withdrawal. Nature 2001;412(6843):141–2. [PubMed: 11449260]

154. Xi ZX, Gilbert JG, Peng XQ, Pak AC, Li X, Gardner EL. Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens. J Neurosci 2006;26(33):8531–6. [PubMed: 16914679]

155. Cohen H. Multiple drug use considered in the light of the stepping-stone hypothesis. Int J Addict 1972;7(1):27–55. [PubMed: 5043838]

156. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood: II. Sequences of progression. Am J Public Health 1984;74(7):668–72. [PubMed: 6742252]

157. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood: III. Predictors of progression. Am J Public Health 1984;74(7):673–81. [PubMed: 6742253]

158. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. J Stud Alcohol 1992;53(5):447–57. [PubMed: 1405637]

159. Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? Addiction 2000;95(4):505–20. [PubMed: 10829327]

160. Van Ours JC. Is cannabis a stepping-stone for cocaine? J Health Econ 2003;22(4):539–54. [PubMed: 12842314]

161. Miller NS, Klahr AL, Gold MS, Sweeney K, Cocores JA. The prevalence of marijuana (cannabis) use and dependence in cocaine dependence. N Y State J Med 1990;90(10):491–2. [PubMed: 2234615]

162. Miller NS, Klahr AL, Gold MS, Sweeney K, Cocores JA, Sweeney DR. Cannabis diagnosis of patients receiving treatment for cocaine dependence. J Subst Abuse 1990;2(1):107–11. [PubMed: 2136098]

163. Agrawal A, Neale MC, Prescott CA, Kendler KS. Cannabis and other illicit drugs: comorbid use and abuse/dependence in males and females. Behav Genet 2004;34(3):217–28. [PubMed: 14990863]

164. Comings DE, Muhleman D, Gade R, Johnson P, Verde R, Saucier G, MacMurray J. Cannabinoid receptor gene (CNR1): association with i.v. drug use. Mol Psychiatry 1997;2(2):161–8. [PubMed: 9106242]

165. Covault J, Gelernter J, Kranzler H. Association study of cannabinoid receptor gene (CNR1) alleles and drug dependence. Mol Psychiatry 2001;6(5):501–2. [PubMed: 11526463]

166. Herman AI, Kranzler HR, Cubells JF, Gelernter J, Covault J. Association study of the CNR1 gene exon 3 alternative promoter region polymorphisms and substance dependence. Am J Med Genet B Neuropsychiatr Genet 2006;141(5):499–503. [PubMed: 16741937]

167. Ballon N, Leroy S, Roy C, Bourdel MC, Charles-Nicolas A, Krebs MO, Poirier MF. (AAT)n repeat in the cannabinoid receptor gene (CNR1): association with cocaine addiction in an African-Caribbean population. Pharmacogenomics J 2006;6(2):126–30. [PubMed: 16314880]

168. Labigalini E Jr, Rodrigues LR, Da Silveira DX. Therapeutic use of cannabis by crack addicts in Brazil. J Psychoactive Drugs 1999;31(4):451–5. [PubMed: 10681113]

169. Aharonovich E, Liu X, Samet S, Nunes E, Waxman R, Hasin D. Postdischarge cannabis use and its relationship to cocaine, alcohol, and heroin use: a prospective study. Am J Psychiatry 2005;162(8):1507–14. [PubMed: 16055773]

170. Hansson AC, Bermudez-Silva FJ, Malinen H, Hyytia P, Sanchez-Vera I, Rimondini R, Rodriguez de Fonseca F, Kunos G, Sommer WH, Heilig M. Genetic impairment of frontocortical endocannabinoid degradation and high alcohol preference. Neuropsychopharmacology 2007;32(1):117–26. [PubMed: 16482090]