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Pharmacology, Biochemistry and Behavior 81 (2005) 396 – 406

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Review

The role of endocannabinoid transmission in cocaine addiction

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Received 18 June 2004; received in revised form 20 December 2004; accepted 23 February 2005

Abstract

Research is beginning to outline a role for the endocannabinoid system in cocaine addiction. Human and animal studies indicate that exogenous cannabinoids modulate the acute rewarding effects of cocaine. These studies, however, cannot directly investigate the necessity of endocannabinoid transmission in cocaine addiction. Studies that do offer a direct assessment show that neither pharmacological antagonism nor deletion of the CB_1 receptor alters the acute rewarding effects of cocaine. In contrast, CB_1 receptors appear to be involved in the association of cocaine reward with environmental cues and reinstatement of cocaine self-administration. Together, these results point to CB_1 receptor antagonists as potential anti-craving compounds in the treatment of cocaine addiction. Given the limitations of human population studies, animal research may be useful in discerning causal inferences between cannabis and cocaine use. While animal research suggests cannabis use may precipitate cocaine relapse, cross-sensitization between cannabinoids and cocaine has not been demonstrated and CB_1 receptors do not mediate behavioral sensitization to cocaine. The effect of acute or chronic cocaine on endocannabinoid transmission in reward-related areas of the brain is relatively under-researched. Acute cocaine administration increases anandamide levels in the striatum, an effect that is mediated by dopamine D_2-like receptors. Conversely, chronic cocaine exposure has no effect on anandamide, but decreases 2-arachidonylglycerol levels in the limbic forebrain. This review highlights research indicating that the endocannabinoid system may subserve certain aspects of cocaine addiction and suggests avenues for future investigation.

Keywords: Endocannabinoid; Cannabinoid; Cocaine; CB_1 receptor; Anandamide; 2-Arachidonylglycerol; Addiction; Dependence; Gateway; Knockout mice; SR 141716

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doi:10.1016/j.pbb.2005.02.015

1. Introduction

Endocannabinoids, such as arachidonylethanolamide (anandamide) and 2-arachidonylglycerol (2-AG), are synthesized in neurons and astrocytes, and are subject to enzymatic degradation by fatty acid amide hydrolase (FAAH) and also high affinity reuptake (Beltramo and Piomelli, 2000; Beltramo et al., 1997; Bisogno et al., 1997, 2001; Desarnaud et al., 1995; Di Marzo et al., 1994, 1998; Stella et al., 1997; Walter et al., 2002). A more detailed picture of the distribution of cannabinoid (CB_1) receptors in discrete brain circuits has been mapped out, especially in reward-related areas of the brain (Freund et al., 2003; Katona et al., 2001; Robbe et al., 2003). Furthermore, endocannabinoids act as retrograde messengers, synthesized on demand and released from the postsynaptic membrane to activate presynaptically located CB_1 receptors that modulate the release of neurotransmitters (Freund et al., 2003; Wilson and Nicoll, 2001).

The science of the endocannabinoid system has advanced our understanding of various disorders of the central nervous system (CNS) (Freund et al., 2003; Porter and Felder, 2001; van der Stelt and Di Marzo, 2003). Converging evidence indicates that the endocannabinoid system is an important constituent of neural substrates involved in drug addiction. For example, human studies have shown that polymorphisms in components of the endocannabinoid system, such as in genes encoding the cannabinoid CB_1 receptor and FAAH, are associated with substance abuse and dependence (Comings et al., 1997; Sipe et al., 2002). Thus, the endocannabinoid system may offer a novel target in the treatment of drug addiction. This may be especially important in the treatment of cocaine abuse and dependence, where no proven effective pharmacotherapies exist (de Lima et al., 2002; van den Brink and van Ree, 2003). Furthermore, a role for endocannabinoid transmission in cocaine addiction might provide a mechanism for the "gateway hypothesis," the view that exposure to cannabis might heighten an individual's susceptibility to becoming dependent on cocaine.

Many studies show commonalities in the neuropharmacological actions of cannabinoids and cocaine, providing prima facie evidence that endocannabinoids might play an important role in cocaine addiction. Administration of cannabinoids or cocaine increases expression of the immediate early gene, *c-fos*, in reward-related brain regions such as the nucleus accumbens (NAc) and the prefrontal cortex (Arnold et al., 2001b; Erdtmann-Vourliotis et al., 1999). Furthermore, exposure to cocaine or the main psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), promotes an increase in the release of DA in the NAc (Carboni et al., 1989; Chen et al., 1990; Hernandez and Hoebel, 1988; Hurd et al., 1989; Pettit and Justice, 1989; Tanda et al., 1997). In addition, injection of either cannabinoids (Hoffman and Lupica, 2001; Manzoni and Bockaert, 2001; Szabo et al., 2002) or cocaine (Nicola et al., 1996) directly into the NAc promotes an inhibition of excitatory synaptic transmission in this brain region.

Cannabinoids interact with CB_1 receptors to produce their rewarding actions, whereas cocaine inhibits monoamine carriers, such as dopamine (DA), serotonin and noradrenaline transporters (Heikkila et al., 1979; Kuhar et al., 1991; Ledent et al., 1999; Maldonado and Rodriguez de Fonseca, 2002; Mansbach et al., 1996; Martellotta et al., 1998; Rothman and Baumann, 2003). As such, evidence of overlap between endocannabinoid and monoamine transmission may also point to a role of endocannabinoids in cocaine dependence. First, mRNA for DA D_1 and D_2 receptors, as well as 5-HT_{1B} receptors, are co-localized with CB_1 receptors in the striatum (Hermann et al., 2002). This co-localization implies that cross-talk may occur between CB_1 and monoamine receptors at the level of signal transduction. In support of this, Glass and Felder (1997) demonstrated that stimulation of either CB_1 receptors or D_2 receptors leads to a decrease in cAMP accumulation. However, an increase in cAMP levels is promoted when these receptors are stimulated together. Similarly, a recent study observed that cells expressing CB_1 receptors alone accumulate less cAMP when exposed to cannabinoids (Jarrahian et al., 2004). When these cells are also transfected with the D_2 receptor gene, cannabinoids act to increase cAMP accumulation. Functional interactions thus exist between the endocannabinoid system and monoamine systems in reward-related areas of the brain.

Nonetheless, a more definitive analysis of the involvement of the endocannabinoid system in cocaine addiction is warranted. The current review will address human and animal experiments that assess whether endocannabinoid transmission plays a role in the habit-forming nature of cocaine. Particular emphasis will be given to animal studies where two main strategies have been implemented. Both approaches infer the functional role of CB_1 receptors, either through pharmacological blockade of CB_1 receptors, or by using transgenic animals engineered to lack the gene encoding the CB_1 receptor (CB_1 receptor knockout mice). Exogenous cannabinoid modulation of cocaine reinforcement will also be overviewed. Such research yields only tentative information on endocannabinoid transmission but may provide directives for future investigations. Finally, behavioral research will be discussed in light of molecular and neurochemical studies which underscore the involvement of endocannabinoid transmission in the neuropharmacological actions of cocaine.

2. The endocannabinoid system and cocaine reward

2.1. Human studies

There exists a paucity of research into the role of the endocannabinoid system in the acute rewarding effects of cocaine. Two human studies provide evidence that canna-

binoids might act to potentiate the euphoriant actions of cocaine. The first of these studies observed that human volunteers who smoked cannabis prior to intravenous (i.v.) cocaine displayed a trend for a prolonged experience of the "high" associated with these drugs (Foltin et al., 1993). Another study revealed that smoking a Δ^9-THC containing cigarette prior to intranasal cocaine decreased the latency to onset of cocaine-induced euphoria and decreased the duration of cocaine's dysphoric effects (Lukas et al., 1994). High doses of Δ^9-THC significantly increased the peak plasma levels and bioavailability of cocaine, possibly due to Δ^9-THC-induced vasodilation of the nasal mucosa. The authors argued that this would attenuate cocaine-induced vasoconstriction, thereby increasing cocaine's absorption. However, it remains possible that pharmacodynamic mechanisms might also explain the apparent interaction between the euphoriant actions of cannabinoids and cocaine.

2.2. Intracranial self-stimulation

Animal studies may provide insight into the pharmacodynamic mechanisms responsible for interactions between the rewarding actions of cannabinoids and cocaine (see Table 1). The intracranial self-stimulation (ICSS) model has enabled the study of the neural and chemical profile of brain reward systems (Wise, 1996). The rate-frequency curve-shift method is the optimal procedure for measuring the rewarding impact of a drug using ICSS (Esposito and Kornetsky, 1977). Typically, animals are trained to bar-press for a series of descending and/or ascending frequencies of electrical stimulation that are supplied to the medial forebrain bundle. The advantage of this method is that it allows the measurement of both the rewarding impact of the stimulation, and also any performance deficits promoted by the drug. Drugs of abuse, such as cocaine, lower the frequency which supports half-maximal rates of responding, i.e., the reward threshold.

Endocannabinoid transmission does not appear to be involved in the acute rewarding effects of cocaine as measured by ICSS. Vlachou et al. (2003) demonstrated that pre-treatment with the CB_1 receptor antagonist, SR 141716 (0.02–0.3 mg/kg) had no effect on the threshold-lowering effects of cocaine (5 mg/kg i.p.) in rats. However, higher doses of SR 141716 may be required to unmask a role of CB_1 receptors in acute cocaine reward given that only doses in excess of 0.3 mg/kg decrease the sensitivity of electrical brain stimulation (Arnold et al., 2001a; Deroche-Gamonet et al., 2001). In any event, CB_1 receptor involvement in ICSS complicates assessment of the role of the endocannabinoid system in the threshold-lowering effects of cocaine.

Vlachou et al. (2003) also reported that the cannabinoid receptor agonist, WIN 55,212-2 (0.3–1 mg/kg i.p.), reversed the threshold-lowering effects of cocaine. This effect is cannabinoid receptor mediated as pre-treatment with SR 141716 reversed the reward-dampening effect of WIN 55,212-2. The effect of WIN 55,515-2 on cocaine reward occurred at doses of WIN 55,212-2 that do not modulate ICSS when administered alone. This is consistent with prior research showing that cannabinoids have no affect on ICSS (Arnold et al., 2001a; Kucharski et al., 1983). However, Gardner and colleagues have shown that Δ^9-THC administration lowers ICSS thresholds in Lewis rats (Gardner and Lowinson, 1991; Gardner and Vorel, 1998). In any case, if CB_1 receptor stimulation does enhance the rewarding impact of ICSS, this would be expected to

Table 1
Endocannabinoid and exogenous cannabinoid modulation of cocaine reward as assessed by animal models of addiction

Model	Species	Treatment	Effect	Authors
Endocannabinoid transmission				
ICSS[a]	Rats	SR 141716	No change	Vlachou et al., 2003
Self-administration	Squirrel monkeys	SR 141716	No change	Tanda et al., 2000
	Rats	SR 141716	No change	De Vries et al., 2001
	Mice	CB1 KO[a]	No change	Cossu et al., 2001
Self-administration: Reinstatement	Rats	SR 141716	Reduced cocaine- and cue- but not stress-primed response rate	De Vries et al., 2001
CPP[a]	Rats	SR 141716	Reversed acquisition but did not alter expression	Chaperon et al., 1998
CPP	Mice	CB1 KO	No change	Martin et al., 2000
Behavioral sensitization	Mice	CB1 KO	No change	Martin et al., 2000
Exogenous cannabinoid modulation				
ICSS	Rats	WIN 55,212-2	Reversed cocaine reward	Vlachou et al., 2003
Self-administration	Rats	WIN 55,212-2	Reduced response rate	Fattore et al., 1999
Self-administration:	Rats	HU 210	Increased cocaine response rate	De Vries et al., 2001
Reinstatement	Rats	Δ^9-THC	No change	Schenk and Partridge, 1999
CPP: Extinction	Rats	Δ^9-THC, cannabidiol	Potentiated extinction	Parker et al., 2004
Cross-sensitization	Rats	CP 55,940	None	Arnold et al., 1998
	Rats	HU 210	None	Ferrari et al., 1999

[a] ICSS—intracranial self-stimulation, CPP—conditioned place preference, KO—knock-out.

enhance the rewarding actions of cocaine by way of an additive interaction of these drugs on the rewarding impact of electrical brain stimulation.

It is difficult to explain the ability of WIN 55,212-2 to reduce the rewarding effects of cocaine on ICSS (Vlachou et al., 2003). One hypothesis is based on research showing CB_1 receptor activation acts as part of an inhibitory feedback mechanism for excessive DA release in the striatum (Giuffrida et al., 1999). Consonant with this, cocaine has recently been shown to increase anandamide levels in the striatum (Centonze et al., 2004). This appears to be due to both an increase in anandamide's synthesis and a decrease in its degradation by FAAH. Increased endocannabinoid transmission was dependent on D_2-like receptor stimulation promoted by cocaine-induced elevations in synaptic DA levels. Further, electrophysiological recordings in striatal slices revealed that cocaine-induced anandamide release inhibited GABA transmission that was partially mediated by CB_1 receptors. In view of this, endocannabinoid transmission may function as a homeostatic mechanism that attempts to offset excessive DA release in the striatum. Thus, the use of exogenous CB_1 receptor agonists in combination with cocaine might instigate this mechanism and attenuate further DA release, consequently decreasing the acute rewarding effects of cocaine.

2.3. Self-administration: acquisition and maintenance

The self-administration model has long been utilized to assess the rewarding actions of cocaine. Drug self-administration studies have shown that animals can be trained to voluntarily self-administer many different drugs of abuse including psychostimulants such as cocaine (LeSage et al., 1999). The advantage of this model is that it most closely resembles the different stages of human drug dependence – acquisition, maintenance and relapse – which has led to a greater understanding of the neurobiological underpinnings of addictive behavior (Balster, 1991; Cami and Farre, 2003; Koob et al., 2004).

Research indicates that the endocannabinoid system does not play a critical role in the acquisition or maintenance of cocaine self-administration. Pre-treatment with SR 141716 fails to modulate cocaine self-administration in either rats or squirrel monkeys (De Vries et al., 2001; Tanda et al., 2000). Similarly, CB_1 receptor knockout mice can be trained to acquire cocaine self-administration behavior (Cossu et al., 2001). It is relevant to note that CB_1 receptor knockout mice do not self-administer morphine, but can be trained to self-administer other drugs of abuse, such as amphetamine and nicotine (Cossu et al., 2001). This finding is consistent with the considerable overlap between endocannabinoid and endogenous opioid systems in the brain, particularly in reward-related circuits (Chen et al., 1990; Gardner, 2002; Tanda and Goldberg, 2003; Tanda et al., 1997; Zimmer et al., 2001). Interestingly, CB_1 receptors play a crucial role in morphine-induced DA release from the NAc (Mascia et al., 1999). However, CB_1 receptors are not critical to cocaine-induced DA release from this reward-related region (referred to in Cossu et al., 2001 as unpublished observations).

While the endocannabinoid system does not mediate cocaine reward, exposure to exogenous cannabinoids appears to modulate cocaine self-administration. Fattore et al. (1999) demonstrated that WIN 55,212-2 (0.25–1 mg/kg i.v.) pre-treatment decreased i.v. self-administration of cocaine using a fixed ratio (FR1) schedule of reinforcement in rats, an effect mediated by CB_1 receptors. Assuming that a decrease in response rate indicates hedonic satiation, such findings suggest that CB_1 receptor activation magnifies the rewarding impact of cocaine. To this degree, given that DA receptor agonists decrease the rate of responding for cocaine in rats, it has been postulated that such agents might be clinically useful in the treatment of cocaine dependence (LeSage et al., 1999). Thus, cannabinoid receptor agonists might also be utilized clinically, acting to decrease the frequency of cocaine use in dependent individuals. Notwithstanding, cannabinoid agents with less abuse liability than WIN 55,212-2 could be used as this compound is self-administered by animals (Fattore et al., 2001).

The opposing effects of WIN 55,212-2 on cocaine reward as measured by Fattore et al. (1999) using the self-administration model and Vlachou et al. (2003) using the ICSS paradigm is challenging to reconcile. However, Fattore et al. (1999) is consistent with earlier human studies showing that cannabinoid exposure potentiates the rewarding impact of cocaine (Foltin et al., 1993; Lukas et al., 1994). Such research parallels investigations showing that the individual administration of Δ^9-THC or cocaine enhances the release of DA from the NAc (Chen et al., 1990; Hernandez and Hoebel, 1988; Hurd et al., 1989; Pettit and Justice, 1989; Tanda et al., 1997). Future investigations could assess whether co-administration of a CB_1 receptor agonist with cocaine acts additively or synergistically to enhance DA release from the NAc, and therefore provide a neural correlate for the action of WIN 55,212-2 on the rate of cocaine self-administration (Fattore et al., 1999).

2.4. Self-administration: reinstatement

Reinstatement of cocaine self-administration is an animal model of relapse observed in cocaine dependent individuals (de Wit and Stewart, 1981; Epstein and Preston, 2003; Gerber and Stretch, 1975). Typically, rats are first trained to self-administer i.v. cocaine before this behavior is extinguished. Following extinction, cocaine self-administration behavior can be reinstated by the presentation of cues (e.g., a tone paired with cocaine), the administration of a cocaine-priming injection, or stress exposure (e.g., footshock). Employing this model, De Vries et al. (2001) demonstrated that pre-treatment with SR 141716 (1–3 mg/kg) reduced reinstatement of cocaine seeking promoted by cocaine-associated cues or cocaine-priming injections, yet failed to

reverse stress-induced reinstatement. Therefore, while the endocannabinoid system does not appear to subserve the acquisition or maintenance of cocaine self-administration, these data suggest that activation of CB_1 receptors is critically involved in relapse to cocaine seeking.

In addition, De Vries et al. (2001) showed that administration of the potent cannabinoid receptor agonist, HU 210 (4–100 μg/kg), dose-dependently promoted reinstatement of cocaine seeking via CB_1 receptor activation. Inconsistent with this, Schenk and Partridge (1999) failed to demonstrate that Δ^9-THC (0.3–3 mg/kg) reinstated cocaine self-administration. The utilization of different cannabinoid receptor agonists might explain these discordant results. The plant-derived Δ^9-THC has a different chemical structure to HU 210, which is a synthetic analogue of Δ^8-THC (Mechoulam et al., 1987; Mechoulam et al., 1988). Consequently, HU 210 has much higher affinity and intrinsic activity at cannabinoid receptors than Δ^9-THC (Howlett et al., 2002). Further, cannabinoid receptor agonists, including HU 210 and Δ^9-THC, appear to have agonist-specific actions on signal transduction pathways that may bestow different behavioral effects (Bonhaus et al., 1998). Methodological differences might also account for these contradictory findings; for example, the period of extinction was much longer in the De Vries et al. (2001) study than in the work of Schenk and Partridge (1999) (14 days versus 3 h). Thus, it is possible the residual pharmacological effects of cocaine may have overshadowed the ability of Δ^9-THC to reinstate cocaine self-administration in the Schenk and Partridge (1999) study.

The mechanism by which the endocannabinoid system subserves cue- and cocaine-, but not stress-primed reinstatement of cocaine self-administration is of interest. Research is emerging that delineates distinct neuronal circuitry underlying reinstated cocaine seeking that is primed by cocaine-related cues, cocaine or stress. It appears that cue-priming relies on DA projections from the ventral tegmental area (VTA) to the basolateral amygdala (BLA), that in turn sends afferent fibres to the prefrontal cortex (Grimm and See, 2000; Kalivas and McFarland, 2003). Cocaine-primed reinstatement seems to be mediated by connections between the VTA and prefrontal cortex (Kalivas and McFarland, 2003). Further, while not well established, stress-primed reinstatement may involve markedly different circuitry, possibly comprised of noradrenergic nerves in the extended amygdala that send projections to the prefrontal cortex via the VTA (Kalivas and McFarland, 2003; McFarland et al., 2004). It is therefore likely that the varied distribution of endocannabinoid mediators and cannabinoid receptors in these circuits might explain the effectiveness of SR 141716 in reversing cue- and cocaine-, but not stress-primed reinstatement of cocaine self-administration.

Much evidence indicates that the mesocorticolimbic DA system is involved in cocaine-primed reinstatement of cocaine self-administration (Kalivas and McFarland, 2003; Shalev et al., 2002; Stewart, 2000). Explanations of how CB_1 receptor blockade impairs cocaine-primed relapse are limited by our insufficient understanding of the role of endocannabinoid transmission in the mesocorticolimbic system. As minimal CB_1 receptor protein or mRNA is expressed in the VTA or the NAc (Egertova and Elphick, 2000; Mailleux and Vanderhaeghen, 1992; Tsou et al., 1998), it is unlikely SR 141716 directly affects neurons in these structures to inhibit cocaine seeking. Nevertheless, structures that innervate the NAc, such as the prefrontal cortex and the BLA, contain higher densities of CB_1 receptors. This has led to investigations into the contribution of such afferent innervation to NAc function (Katona et al., 2001; Pistis et al., 2004; Robbe et al., 2001).

Such research has provided a new conceptualization for how cannabinoids engender their rewarding effects (Robbe et al., 2001; van der Stelt and Di Marzo, 2003). According to this model, cannabinoids act on presynaptic CB_1 receptors found on cortical glutamatergic afferents to the NAc (Robbe et al., 2001). The ensuing decrease in glutamate release is proposed to restrain the inhibitory action that GABAergic medium spiny neurons have on the VTA. Consequently, disinhibition of the VTA would lead to DA release downstream in the NAc (Szabo et al., 2002). Thus, HU 210 may increase the release of DA in the NAc and act as a trigger to reinstate cocaine seeking (De Vries et al., 2001). Conversely, assuming significant endocannabinoid tone, blockade of presynaptic CB_1 receptors with SR 141716 at the cortical-NAc synapse might promote glutamate release, initiating enhanced GABAergic transmission and thus inhibition of the VTA. As DA is an important mediator of cocaine-primed relapse (Shalev et al., 2002), the resulting decrease in DA release from the NAc might attenuate necessary synaptic transmission for cocaine relapse. Unfortunately, this theory might over-emphasize the role of DA in cocaine-primed reinstatement with mounting evidence supporting the notion that glutamate might contribute more than DA (Cornish et al., 1999; Cornish and Kalivas, 2000; Kalivas, 2004). Clearly, the specific nature of endocannabinoid involvement in the reinstatement of cocaine seeking needs to be further examined.

The De Vries et al. (2001) study has two far-reaching implications. First, it implies that cannabinoid consumption may enhance vulnerability to cocaine seeking in humans. Indeed, one clinical study demonstrates that prior cannabis use hastens relapse in abstinent cocaine dependent individuals (Rawson et al., 1986). Accordingly, treatment programs could adopt strategies to prevent cannabis use in abstinent cocaine users. Such developments will be assisted by research that further characterizes the phenomenon of cannabinoid-induced cocaine seeking in humans. The second implication of the De Vries et al. (2001) study is that CB_1 receptor antagonists, such as SR 141716, may prove useful in the pharmacotherapy of cocaine addiction. While many compounds have been trialed to reduce cocaine relapse, none have yet been established as effective (de

Lima et al., 2002; van den Brink and van Ree, 2003). CB_1 receptor antagonists may thus provide new therapeutic candidates in relapse prevention for cocaine addiction.

2.5. Conditioned place preference

The role of the endocannabinoid system in cocaine-induced conditioned place preference (CPP) has been investigated in several studies. CPP assesses the perception of the rewarding value of reinforcers (Carr et al., 1989; Chaperon and Thiebot, 1999). Animals are subjected to a conditioning phase where they are injected with a drug of abuse or vehicle on alternate days and then placed in a distinctive environment for each injection. Control animals are injected with vehicle on every day. Following conditioning, animals are tested drug-free, with rats expressing a preference for the drug-paired environment over the vehicle-paired one. Drug-seeking behavior is therefore elicited by environmental cues associated with the rewarding effects of a drug.

The first of these studies indicates that endocannabinoid transmission mediates the association of the rewarding effects of cocaine with environmental cues. Co-administration of SR 141716 with cocaine in the conditioning phase abolishes the acquisition of CPP to cocaine in rats (Chaperon et al., 1998). However, Martin et al. (2000) demonstrated cocaine-induced CPP in CB_1 receptor knockout mice. It is possible that such contradictory observations could be due to species differences. Alternatively, CB_1 receptor knockout mice may express adaptations that compensate for the functional loss of this receptor from the earliest stages of development (Crawley, 1999). A further explanation is based on the inverse agonist properties of SR 141716 (Bouaboula et al., 1997; Seifert and Wenzel-Seifert, 2002). Constitutively active CB_1 receptors may be critical to CPP to cocaine. This activity may be reversed by the administration of SR 141716 that shifts the CB_1 receptor into an inactive conformation.

A final view that might explain the disparate findings of Chaperon et al. (1998) and Martin et al. (2000) is based on recent evidence indicating SR 141716 might antagonize, in addition to the CB_1 receptor, an uncharacterized cannabinoid receptor that is located in the CNS (Freund et al., 2003; Hajos et al., 2001; Pistis et al., 2004). If this unknown cannabinoid receptor was solely responsible for cocaine-induced CPP, then this would explain why pharmacological blockade of this receptor with SR 141716, but not targeted deletion of the CB_1 receptor, impairs the acquisition of CPP to cocaine. Future studies could observe whether the administration of selective CB_1 receptor antagonists, such as AM 251 (Pistis et al., 2004), are also ineffective in modulating cocaine-induced CPP. Further, if indeed an additional cannabinoid receptor is cloned, it could be examined whether animals lacking the gene for this receptor do not express cocaine-induced CPP.

It has recently been reported that the endocannabinoid system might be involved in extinction of CPP to cocaine (Parker et al., 2004). Low doses of the plant-derived cannabinoids, Δ^9-THC and cannabidiol, potentiate extinction of cocaine-induced CPP. The results of Parker et al. (2004) are consistent with a critical role for the endocannabinoid system in the extinction of conditioned fear (Marsicano et al., 2002). However, these findings are inconsistent with cannabinoid-induced relapse to cocaine seeking (De Vries et al., 2001), as the results of Parker et al. (2004) imply cannabinoid administration would decrease the propensity to relapse from exposure to cocaine associated cues. The different cannabinoid receptor agonists used in these studies might explain this contradiction. In addition, the mechanisms responsible for extinction of cocaine CPP may be distinct from those involved in cannabinoid-primed reinstatement of cocaine seeking (Parker et al., 2004).

3. The endocannabinoid system and neuroadaptive change: cocaine sensitization

Neuroadaptations in the mesolimbic DA system that accompany chronic drug use offer an explanation for why drug abusers frequently relapse after discontinuing use (Koob, 1996; Koob et al., 2004; Robbins and Everitt, 1999; Robinson and Berridge, 1993). In the field of neuropharmacology, sensitization of the mesolimbic DA system is thought to herald the expression of such neuroadaptations. Accordingly, repeated intermittent exposure to drugs such as cocaine, amphetamine, nicotine or heroin produces progressively greater drug-induced increases in DA efflux in the NAc, a phenomenon referred to as neurochemical sensitization. This is coupled to a progressively greater locomotor response to the drug (behavioral sensitization) and increased positively reinforcing effects of the drug and drug-related cues (incentive sensitization).

Only one study has directly examined whether the endocannabinoid system is implicated in behavioral sensitization to cocaine. Martin et al. (2000) reported that behavioral sensitization to cocaine occurs in CB_1 receptor knockout mice. In contrast, these same animals did not develop behavioral sensitization to morphine, reaffirming the important role CB_1 receptors have in the habit-forming nature of opioids (Cadoni et al., 2001; Chen et al., 1990; Maldonado and Rodriguez de Fonseca, 2002; Mascia et al., 1999; Tanda et al., 1997). It is possible, however, that compensatory adaptations in knockout mice might make the CB_1 receptor redundant in behavioral sensitization to cocaine. To avoid such problems, CB_1 receptor antagonists could be utilized in future studies. Furthermore, it would be interesting to assess whether a progressive increase in endocannabinoid release occurs in reward-related areas of the brain, such as the striatum, in animals undergoing behavioral sensitization to cocaine.

One mechanism thought to be responsible for sensitization to the locomotor-stimulant effects of cocaine is long-term depression (LTD) in the NAc (Thomas et al., 2001). This form of experience-dependent synaptic plasticity has been proposed to contribute to neuroadaptations that subserve addictive behavior (Gerdeman et al., 2003). LTD is promoted by high frequency stimulation of glutamatergic afferents to medium spiny neurons in the striatum. Consequently, the NAc becomes refractory to excitatory input through long-term inhibition of glutamate release. Studies indicate anandamide is critically involved in LTD by acting as a retrograde messenger and activating presynaptically located CB_1 receptors (Gerdeman et al., 2002; Robbe et al., 2002). It is noteworthy that CB_1 receptors mediate amphetamine-induced LTD at synapses in the amygdala (Huang et al., 2003). However, at this point in time, no studies have assessed whether cocaine-induced LTD requires endocannabinoid transmission in the striatum.

Research has examined modulation of the endocannabinoid system in animals undergoing chronic treatment with cocaine. In two related studies, endocannabinoid and CB_1 receptor levels were analysed in the CNS of rats following administration of cocaine (15 mg/kg) twice daily for 10 days (Gonzalez et al., 2002a,b). Compared to pre-treatment with nicotine and ethanol, cocaine had the smallest impact on endocannabinoid levels in the brain (Gonzalez et al., 2002a). Cocaine promoted a significant decrease in 2-AG levels in the limbic forebrain (this includes the NAc and the BLA). However, no change was observed in levels of anandamide in the same brain region. Anandamide and 2-AG levels in other reward-related areas of the CNS, such as the midbrain, striatum and the cerebral cortex, were all unaffected by chronic cocaine exposure.

The second of these studies measured the effects of chronic cocaine on CB_1 receptor protein and mRNA levels using autoradiography and in situ hybridization respectively (Gonzalez et al., 2002b). Consistent with their previous study, differences were observed between cocaine and the other drugs examined, morphine and alcohol. This suggests that endocannabinoids have a diverse role in the habit-forming nature of drugs of abuse, rather than a simple, common role across all drug classes. Chronic pre-treatment with cocaine altered CB_1 receptor mRNA levels in the ventromedial hypothalamus and the superficial and deep layers of the cerebral cortex. Reward-related structures in the limbic forebrain were unaffected in either mRNA or CB_1 receptor levels. It was concluded that while chronic cocaine administration does not affect the basal level of CB_1 receptors, it might inhibit gene transcription or mRNA stability. Nonetheless, it is possible that alterations in CB_1 receptor levels may be expressed at a later time than examined in this study. Interestingly, neuroadaptations associated with behavioral sensitization may arise weeks or months following cocaine withdrawal (Vezina, 2004). Indeed, long-term depression is observed at cortico-NAc synapses weeks after the cessation of a schedule of administration that promoted behavioral sensitization to cocaine (Thomas et al., 2001). Accordingly, more pronounced alterations in the endocannabinoid system may occur after a longer withdrawal period from cocaine administration.

4. The “gateway” theory

The “gateway” theory, a phenomenon often alleged by politicians, holds that cannabis use may predispose users to the administration of other “harder” drugs of abuse, such as cocaine. The most extensive research pertinent to the gateway theory are longitudinal studies conducted by Kandel and colleagues (Kandel et al., 1997; Kandel and Yamaguchi, 1993; Kandel and Davies, 1992). These researchers uncovered a highly predictable sequence of drug use in American adolescents which starts with alcohol and tobacco, is followed by cannabis (which is almost invariably the first illicit drug used) then hallucinogens and tranquilizers, before finally moving to cocaine or heroin.

While human population data indicate that cannabis use is associated with cocaine use, it is very difficult to claim cannabis use per se causes cocaine use (Kandel, 2003; Morral et al., 2002). One recent study explored this causative link by using a large sample of Australian twins (Lynskey et al., 2003). It was hypothesized that if cannabis use does not cause cocaine use, the risk of using cocaine should be the same for early initiating cannabis users compared to their discordant co-twins who began using cannabis later in life. However, it was found that early initiating cannabis users were more likely than their discordant co-twins to become dependent on cocaine. Therefore, it was hesitantly concluded that cannabis use causes a progression to cocaine use and dependence. Nonetheless, many early initiating cannabis users did not progress to cocaine use and dependence, and it has also been noted that the distinct life experiences of twins may in part explain the results (Kandel, 2003).

While the assertion that cannabis use causes cocaine use is contentious, the association of cannabis exposure and cocaine use may arise for many reasons. One possibility is that cannabis use may expose human users to a social “gateway” where drugs such as cocaine become more accessible via the criminal social nexus through which cannabis is obtained. This is the fundamental premise that has underpinned the de facto decriminalization of cannabis in The Netherlands where the dissociation of cannabis supply from the supply of “harder” drugs has been a primary aim. Interestingly, it appears this strategy has been at least partially achieved, with cannabis users in the US being more likely to acquire a cocaine addiction than their counterparts in The Netherlands (MacCoun and Reuter, 2001). Alternatively, a common underlying factor, such as a “drug using propensity,” might explain the cannabis “gateway” phenomenon (Morral et al., 2002). This factor could

be comprised of various genetic and environmental characteristics. Thus, the correlation between cannabis use and cocaine use may reflect no more than a global vulnerability to addiction in these persons. A third possible explanation, that does not necessarily exclude the first two, is that cannabis use affects the mesolimbic DA system so that the user is "sensitized" to becoming dependent on another substance (Robinson and Berridge, 1993).

In animal research, pre-exposure to one drug may also sensitize rats to the behavioral, neurochemical and incentive effects of another drug (cross-sensitization) and it is this phenomenon that offers a model of the "gateway" effects presumed to occur in humans. Minimal research has examined whether chronic cannabinoid exposure can "cross-sensitize" the effects of other drugs. From the studies that have been conducted, it appears that cross-sensitization occurs between cannabinoids and morphine, or cannabinoids and amphetamine (Cadoni et al., 2001; Gorriti et al., 1999; Lamarque et al., 2001). However, studies assessing interactions between cannabinoids and cocaine have failed to demonstrate cross-sensitization (Arnold et al., 1998; Ferrari et al., 1999). Such results are consistent with the lack of CB_1 receptor involvement in behavioral sensitization to cocaine (Martin et al., 2000).

The first study conducted in this area examined cross-sensitization between cannabinoids and cocaine in a number of ways (Arnold et al., 1998). Following intermittent exposure to the cannabinoid receptor agonist, CP 55,940 (10–50 μg/kg i.p.), no augmented locomotor response to cocaine (15 mg/kg i.p.) was observed in cannabinoid pre-treated rats. Similarly, animals intermittently administered cocaine did not show any alteration in the locomotor-depressant actions of CP 55,940 following a challenge injection. As such, cross-sensitization was not observed in either the cannabinoid–cocaine or cocaine–cannabinoid direction. Furthermore, when CP 55,940 was co-administered with cocaine under an intermittent schedule of administration, this reduced, but did not completely abolish, the progressive increase in the locomotor-stimulant effects of cocaine. However, this co-administration of cocaine and CP 55,940 did not inhibit the development of behavioral sensitization to cocaine, as no difference was observed between the cocaine pre-treated and the cocaine–cannabinoid co-administration groups when both were challenged with cocaine alone. The findings of Arnold et al. (1998) are consistent with a later study by Ferrari et al. (1999) who did not observe cross-sensitization between cocaine and HU 210 (6.25–100 μg/kg i.p.) using a similar methodology.

It is perplexing why cross-sensitization with cannabinoids can be demonstrated for amphetamine but not cocaine. One possible reason is based on differences in the mechanism of action of these drugs. While cocaine inhibits monoamine transporters (Reith et al., 1986, 1997; Rocha et al., 1998), amphetamine causes the release of DA from vesicles and reverses the action of the DA transporter (Heikkila et al., 1975; Jones et al., 1998; Liang and Rutledge, 1982; Raiteri et al., 1975). This in turn promotes a much greater extracellular level of DA than that observed following cocaine administration (Carboni et al., 1989; Carboni et al., 2001). Therefore, the ability of amphetamine to promote markedly greater extracellular DA levels may provide sufficient neurochemical conditions supportive of cross-sensitization to cannabinoids. It is also possible that previous studies investigating cross-sensitization between cannabinoids and cocaine have not implemented the correct experimental conditions to reveal such an effect. Studies illustrating cross-sensitization between cannabinoids and amphetamine used Δ^9-THC, rather than synthetic cannabinoid receptor agonists, which was administered at higher doses and under a distinct schedule of administration (Gorriti et al., 1999; Lamarque et al., 2001). Further, Lamarque et al. (2001) demonstrated cross-sensitization within a narrow period of time and only in a drug-preferring sub-population of Sprague–Dawley rats. Moreover, Gorriti et al. (1999) used more elaborate measures of behavior and utilized various doses of the challenge injection, offering a wider range to detect cross-sensitization.

5. Conclusion

This review highlights that endocannabinoid transmission subserves different aspects of cocaine addiction. Evidence to date suggests that the endocannabinoid system is not involved in the acute rewarding effects of cocaine. In contrast, CB_1 receptors may mediate the association of cocaine reward with environmental cues and reinstatement of cocaine self-administration. Cannabis use in humans may thus precipitate relapse and CB_1 receptor antagonists may prove to be effective in preventing relapse in cocaine addiction. Further advances in our understanding of the endocannabinoid system's role in the actions of cocaine may provide new avenues in the pharmacotherapy of cocaine abuse and dependence.

Acknowledgements

I am grateful to Dr. Kirsten Morley for her valuable comments on the manuscript.

References

Arnold 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;354:9–16.

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 2001a;70:97–108.

Arnold JC, Topple AN, Mallet PE, Hunt GE, McGregor IS. The distribution of cannabinoid-induced Fos expression in rat brain: differences between the Lewis and Wistar strain. Brain Res 2001b;921:240–55.

Balster RL. Drug abuse potential evaluation in animals. Br J Addict 1991; 86:1549–58.
Beltramo M, Piomelli D. Carrier-mediated transport and enzymatic hydrolysis of the endogenous cannabinoid 2-arachidonylglycerol. Neuroreport 2000;11:1231–5.
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;277:1094–7.
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(2):671–7.
Bisogno T, Maccarrone M, De Petrocellis L, Jarrahian A, Finazzi-Agro A, Hillard C, et al. The uptake by cells of 2-arachidonoylglycerol, an endogenous agonist of cannabinoid receptors. Eur J Biochem 2001; 268:1982–9.
Bonhaus DW, Chang LK, Kwan J, Martin GR. Dual activation and inhibition of adenylyl cyclase by cannabinoid receptor agonists: evidence for agonist-specific trafficking of intracellular responses. J Pharmacol Exp Ther 1998;287(3):884–8.
Bouaboula M, Perrachon S, Milligan L, Canat X, Rinaldi-Carmona M, Portier M, et al. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1 Evidence for a new model of receptor/ligand interactions. J Biol Chem 1997;272:22330–9.
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 (Berl) 2001;158:259–66.
Cami J, Farre M. Drug addiction. N Engl J Med 2003;349:975–86.
Carboni E, Imperato A, Perezzani L, Di Chiara G. Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 1989;28(3):653–61.
Carboni E, Spielewoy C, Vacca C, Nosten-Bertrand M, Giros B, Di Chiara G. Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene. J Neurosci 2001;21(9):1–4 [RC141].
Carr GD, Fibiger HC, Phillips AC. Conditioned place preference as a measure of drug reward. In: Liebman JM, Cooper SJ, editors. The neuropharmacological basis of reward. Oxford: Clarendon Press; 1989.
Centonze D, Battista N, Rossi S, Mercuri NB, Finazzi-Agro A, Bernardi G, et al. A critical interaction between dopamine D2 receptors and endocannabinoids mediates the effects of cocaine on striatal GABAergic transmission. Neuropsychopharmacology 2004;29(8):1488–97.
Chaperon F, Thiebot MH. Behavioral effects of cannabinoid agents in animals. Crit Rev Neurobiol 1999;13:243–81.
Chaperon F, Soubrie P, Puech AJ, Thiebot MH. Involvement of central cannabinoid (CB1) receptors in the establishment of place conditioning in rats. Psychopharmacology (Berl) 1998;135:324–32.
Chen JP, Paredes W, Li J, Smith D, Lowinson J, Gardner EL. Delta 9-tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis. Psychopharmacology 1990;102:156–62.
Comings DE, Muhleman D, Gade R, Johnson P, Verde R, Saucier G, et al. Cannabinoid receptor gene (*CNR1*): association with IV drug use. Mol Psychiatry 1997;2:161–8.
Cornish JL, Kalivas PW. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. J Neurosci 2000;20:RC89.
Cornish JL, Duffy P, Kalivas PW. A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. Neuroscience 1999;93:1359–67.
Cossu G, Ledent C, Fattore L, Imperato A, Bohme GA, Parmentier M, et al. Cannabinoid CB1 receptor knockout mice fail to self-administer morphine but not other drugs of abuse. Behav Brain Res 2001;118: 61–5.
Crawley JN. Behavioral phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioral tests. Brain Res 1999;835(1): 18–26.
de Lima MS, De Oliveira Soares BG, Reisser AA, Farrell M. Pharmacological treatment of cocaine dependence: a systematic review. Addiction 2002;97:931–49.
De Vries TJ, Shaham Y, Homberg JR, Crombag H, Schuurman K, Dieben J, et al. A cannabinoid mechanism in relapse to cocaine seeking. Nat Med 2001;7:1151–4.
de Wit H, Stewart J. Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology (Berl) 1981;75(2):134–43.
Deroche-Gamonet V, Le Moal M, Piazza PV, Soubrie P. SR141716, a CB1 receptor antagonist, decreases the sensitivity to the reinforcing effects of electrical brain stimulation in rats. Eur J Pharmacol 2001;430:49–58.
Desarnaud F, Cadas H, Piomelli D. Anandamide amidohydrolase activity in rat brain microsomes Identification and partial characterization. J Biol Chem 1995;270:6030–5.
Di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz J, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 1994;372:686–91.
Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends Neurosci 1998;21:521–8.
Egertova M, Elphick MR. Localisation of cannabinoid receptors in the rat brain using antibodies to the intracellular C-terminal tail of CB. J Comp Neurol 2000;422:159–71.
Epstein DH, Preston KL. The reinstatement model and relapse prevention: a clinical perspective. Psychopharmacology (Berl) 2003;168:31–41.
Erdtmann-Vourliotis M, Mayer P, Riechert U, Hollt V. Acute injection of drugs with low addictive potential (delta(9)-tetrahydrocannabinol, 3,4-methylenedioxymethamphetamine, lysergic acid diamide) causes a much higher *c-fos* expression in limbic brain areas than highly addicting drugs (cocaine and morphine). Mol Brain Res 1999;71:313–24.
Esposito R, Kornetsky C. Morphine lowering of self-stimulation thresholds: lack of tolerance with long-term administration. Science 1977; 195(4274):189–91.
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.
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;156:410–6.
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;65:823–31.
Foltin RW, Fischman MW, Pippen PA, Kelly TH. Behavioral effects of cocaine alone and in combination with ethanol or marijuana in humans. Drug Alcohol Depend 1993;32:93–106.
Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83:1017–66.
Gardner EL. Addictive potential of cannabinoids: the underlying neurobiology. Chem Phys Lipids 2002;121:267–90.
Gardner EL, Lowinson JH. Marijuana's interaction with brain reward systems: update 1991. Pharmacol Biochem Behav 1991;40:571–80.
Gardner EL, Vorel SR. Cannabinoid transmission and reward-related events. Neurobiol Dis 1998;5:502–33.
Gerber GJ, Stretch R. Drug-induced reinstatement of extinguished self-administration behavior in monkeys. Pharmacol Biochem Behav 1975; 3(6):1055–61.
Gerdeman GL, Ronesi J, Lovinger DM. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. Nat Neurosci 2002;5:446–51.
Gerdeman GL, Partridge JG, Lupica CR, Lovinger DM. It could be habit forming: drugs of abuse and striatal synaptic plasticity. Trends Neurosci 2003;26:184–92.

Giuffrida A, Parsons LH, Kerr TM, de Fonseca FR, Navarro M, Piomelli D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. Nat Neurosci 1999;2:358–63.

Glass M, Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. J Neurosci 1997;17:5327–33.

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 2002a; 954:73–81.

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 2002b;66:77–84.

Gorriti MA, de Fonseca FR, Navarro M, Palomo T. Chronic (−)-Delta(9-)tetrahydrocannabinol treatment induces sensitization to the psychomotor effects of amphetamine in rats. Eur J Pharmacol 1999; 365:133–42.

Grimm JW, See RE. Dissociation of primary and secondary reward-relevant limbic nuclei in an animal model of relapse. Neuropsychopharmacology 2000;22:473–9.

Hajos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. Neuroscience 2001;106:1–4.

Heikkila RE, Orlansky H, Mytilineou C, Cohen G. Amphetamine: evaluation of D- and L-isomers as releasing agents and uptake inhibitors for 3H-dopamine and 3H-norepinephrine in slices of rat neostriatum and cerebral cortex. J Pharmacol Exp Ther 1975;194(1):47–56.

Heikkila RE, Cabbat FS, Manzino L, Duvoisin RC. Rotational behavior induced by cocaine analogs in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra: dependence upon dopamine uptake inhibition. J Pharmacol Exp Ther 1979;211(1):189–94.

Hermann H, Marsicano G, Lutz B. Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience 2002;109:451–60.

Hernandez L, Hoebel BG. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci 1988;42:1705–12.

Hoffman AF, Lupica CR. Direct actions of cannabinoids on synaptic transmission in the nucleus accumbens: a comparison with opioids. J Neurophysiol 2001;85:72–83.

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. International Union of Pharmacology: XXVII Classification of cannabinoid receptors. Pharmacol Rev 2002;54:161–202.

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: 10311–20.

Hurd YL, Weiss F, Koob GF, And NE, Ungerstedt U. Cocaine reinforcement and extracellular dopamine overflow in rat nucleus accumbens: an in vivo microdialysis study. Brain Res 1989;498:199–203.

Jarrahian A, Watts VJ, Barker EL. D2 dopamine receptors modulate Gα-subunit coupling of the CB1 cannabinoid receptor. J Pharmacol Exp Ther 2004;308:880–6.

Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. J Neurosci 1998;18(6):1979–86.

Kalivas PW. Glutamate systems in cocaine addiction. Curr Opin Pharmacol 2004;4:23–9.

Kalivas PW, McFarland K. Brain circuitry and the reinstatement of cocaine-seeking behavior. Psychopharmacology (Berl) 2003;168:44–56.

Kandel DB. Does marijuana use cause the use of other drugs? JAMA 2003; 289:482–3.

Kandel DB, Davies M. Progression to regular marijuana involvement: phenomenology and risk factors for near-daily use. In: Glantz M, Pickens R, editors. Vulnerability to drug abuse. Washington (DC): American Psychological Association; 1992.

Kandel D, Yamaguchi K. From beer to crack: developmental patterns of drug involvement. Am J Public Health 1993;83:851–5.

Kandel D, Chen K, Warner LA, Kessler RC, Grant B. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the US population. Drug Alcohol Depen 1997;44:11–29.

Katona I, Rancz EA, Acsady L, Ledent C, Mackie K, Hajos N, et al. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. J Neurosci 2001;21: 9506–18.

Koob GF. Drug addiction: the yin and yang of hedonic homeostasis. Neuron 1996;16:893–5.

Koob GF, Ahmed SH, Boutrel B, Chen SA, Kenny PJ, Markou A, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev 2004;27:739–49.

Kucharski LT, Williams JEG, Kornetsky C. The effects of levonantradol on rewarding brain stimulation thresholds in the rat. Pharmacol Biochem Behav 1983;19:149–51.

Kuhar MJ, Ritz MC, Boja JW. The dopamine hypothesis of the reinforcing properties of cocaine. Trends Neurosci 1991;14(7):299–302.

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;41:118–29.

Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 1999;283(5400): 401–4.

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: 717–41.

Liang NY, Rutledge CO. Evidence for carrier-mediated efflux of dopamine from corpus striatum. Biochem Pharmacol 1982;31(15):2479–84.

Lukas SE, Sholar M, Kouri E, Fukuzako H, Mendelson JH. Marihuana smoking increases plasma cocaine levels and subjective reports of euphoria in male volunteers. Pharmacol Biochem Behav 1994;48: 715–21.

Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PA, Nelson EC, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. JAMA 2003;289:427–33.

MacCoun R, Reuter P. Evaluating alternative cannabis regimes. Br J Psychiatry 2001;178:123–8.

Mailleux P, Vanderhaeghen JJ. Distribution of neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and in situ hybridization histochemistry. Neuroscience 1992;48:655–68.

Maldonado R, Rodriguez de Fonseca F. Cannabinoid addiction: behavioral models and neural correlates. J Neurosci 2002;22:3326–31.

Mansbach RS, Rovetti CC, Winston EN, Lowe 3rd JA. Effects of the cannabinoid CB1 receptor antagonist SR141716A on the behavior of pigeons and rats. Psychopharmacology (Berl) 1996;124(4):315–22.

Manzoni OJ, Bockaert J. Cannabinoids inhibit GABAergic synaptic transmission in mice nucleus accumbens. Eur J Pharmacol 2001;412: R3–5.

Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, et al. The endogenous cannabinoid system controls extinction of aversive memories. Nature 2002;418:530–4.

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(2):327–30.

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.

Mascia MS, Obinu MC, Ledent C, Parmentier M, Bohme GA, Imperato A, et al. Lack of morphine-induced dopamine release in the nucleus accumbens of cannabinoid CB(1) receptor knockout mice. Eur J Pharmacol 1999;383:R1–2.

McFarland K, Davidge SB, Lapish CC, Kalivas PW. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. J Neurosci 2004;24:1551–60.

Mechoulam R, Lander N, Srebnik M, Breuer A, Segal M, Feigenbaum JJ, et al. Stereochemical requirements for cannabimimetic activity. NIDA Res Monogr 1987;79:15–30.

Mechoulam R, Feigenbaum JJ, Lander N, Segal M, Jarbe TU, Hiltunen AJ, et al. Enantiomeric cannabinoids: stereospecificity of psychotropic activity. Experientia 1988;44(9):762–4.

Morral AR, McCaffrey DF, Paddock SM. Reassessing the marijuana gateway effect. Addiction 2002;97:1493–504.

Nicola SM, Kombian SB, Malenka RC. Psychostimulants depress excitatory synaptic transmission in the nucleus accumbens via presynaptic D1-like dopamine receptors. J Neurosci 1996;16:1591–604.

Parker LA, Burton P, Sorge RE, Yakiwchuk C, Mechoulam R. Effect of low doses of Delta(9)-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. Psychopharmacology (Berl) 2004;175(3): 360–6.

Pettit HO, Justice Jr JB. Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacol Biochem Behav 1989;34:899–904.

Pistis M, Perra S, Pillolla G, Melis M, Gessa GL, Muntoni AL. Cannabinoids modulate neuronal firing in the rat basolateral amygdala: evidence for CB1- and non-CB1-mediated actions. Neuropharmacology 2004;46:115–25.

Porter AC, Felder CC. The endocannabinoid nervous system: unique opportunities for therapeutic intervention. Pharmacol Ther 2001;90: 45–60.

Raiteri M, Bertollini A, Angelini F, Levi G. D-Amphetamine as a releaser or reuptake inhibitor of biogenic amines in synaptosomes. Eur J Pharmacol 1975;34(1):189–95.

Rawson RA, Obert JL, McCann MJ, Mann AJ. Cocaine treatment outcome: cocaine use following inpatient, outpatient, and no treatment. NIDA Res Monogr 1986;67:271–7.

Reith ME, Meisler BE, Sershen H, Lajtha A. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Biochem Pharmacol 1986];35(7):1123–9.

Reith ME, Li MY, Yan QS. Extracellular dopamine, norepinephrine, and serotonin in the ventral tegmental area and nucleus accumbens of freely moving rats during intracerebral dialysis following systemic administration of cocaine and other uptake blockers. Psychopharmacology (Berl) 1997;134(3):309–17.

Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ. Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. J Neurosci 2001;21:109–16.

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 U S A 2002;99:8384–8.

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.

Robbins TW, Everitt BJ. Drug addiction: bad habits add up. Nature 1999; 398:567–70.

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993;18:247–91.

Rocha BA, Fumagalli F, Gainetdinov RR, Jones SR, Ator R, Giros B, et al. Cocaine self-administration in dopamine-transporter knockout mice. Nat Neurosci 1998;1(2):132–7.

Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. Eur J Pharmacol 2003;479:23–40.

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

Seifert R, Wenzel-Seifert K. Constitutive activity of G-protein-coupled receptors: cause of disease and common property of wild-type receptors. Naunyn Schmiedebergs Arch Pharmacol 2002;366:381–416.

Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. Pharmacol Rev 2002;54:1–42.

Sipe JC, Chiang K, Gerber AL, Beutler E, Cravatt BF. A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proc Natl Acad Sci U S A 2002;99:8394–9.

Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. Nature 1997;388:773–8.

Stewart J. Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. J Psychiatry Neurosci 2000;25:125–36.

Szabo B, Siemes S, Wallmichrath I. Inhibition of GABAergic neurotransmission in the ventral tegmental area by cannabinoids. Eur J Neurosci 2002;15:2057–61.

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

Tanda G, Pontieri FE, DI Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. Science 1997;276:2048–50.

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.

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;4:1217–23.

Tsou K, Brown S, Sanudo-Pena C, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 1998;83(2):393–411.

van den Brink W, van Ree JM. Pharmacological treatments for heroin and cocaine addiction. Eur Neuropsychopharmacol 2003;13:476–87.

van der Stelt M, Di Marzo V. The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. Eur J Pharmacol 2003;480:133–50.

Vezina P. Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychomotor stimulant drugs. Neurosci Biobehav Rev 2004;27:827–39.

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;141:215–22.

Walter L, Franklin A, Witting A, Moller T, Stella N. Astrocytes in culture produce anandamide and other acylethanolamides. J Biol Chem 2002; 277:20869–76.

Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 2001;410:588–92.

Wise RA. Addictive drugs and brain stimulation reward. Annu Rev Neurosci 1996;19:319–40.

Zimmer A, Valjent E, Konig M, Zimmer AM, Robledo P, Hahn H, et al. Absence of delta-9-tetrahydrocannabinol dysphoric effects in dynorphin-deficient mice. J Neurosci 2001;21:9499–505.