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Review

Endocannabinoid signaling system and brain reward: Emphasis on dopamine

Eliot L. Gardner*

Neuropsychopharmacology Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Building C-Room 393, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA

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Abstract

The brain's reward circuitry consists of an "in series" circuit of dopaminergic (DA) neurons in the ventral tegmental area (VTA), nucleus accumbens (Acb), and that portion of the medial forebrain bundle (MFB) which links the VTA and Acb. Drugs which enhance brain reward (and have derivative addictive potential) have common actions on this core DA reward system and on animal behaviors relating to its function. Such drugs enhance electrical brain-stimulation reward in this reward system; enhance neural firing and DA tone within it; produce conditioned place preference (CPP), a behavioral model of incentive motivation; are self-administered; and trigger reinstatement of drug-seeking behavior in animals extinguished from drug self-administration. Cannabinoids were long considered different from other reward-enhancing drugs in reward efficacy and in underlying neurobiological substrates activated. However, it is now clear that cannabinoids activate these brain reward processes and reward-related behaviors in similar fashion to other reward-enhancing drugs. This brief review discusses the roles that endogenous cannabinoids (especially activation of the CB1 receptor) may play within the core reward system, and concludes that while cannabinoids activate the reward pathways in a manner consistent with other reward-enhancing drugs, the neural mechanisms by which this occurs may differ. Published by Elsevier Inc.

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Contents

Abbreviations: Acb, nucleus accumbens; 2-AG, 2-arachidonylglycerol; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; BSR, brain-stimulation reward; CeA, central nucleus of the amygdala; CPA, conditioned place aversion; CPP, conditioned place preference; CRF, corticotropin releasing factor; DA, dopamine, dopaminergic; GABA, gamma-aminobutryic acid; LTD, long-term depression; LTP, long-term potentiation; MFB, medial forebrain bundle; mGluR5, metabotropic glutamate type 5 receptor; MPFC, medial prefrontal cortex; 3-MT, 3-methoxytyramine; PR, progressive ratio; THC, Δ^9-tetrahydrocannabinol; VP, ventral pallidum; VTA, ventral tegmental area; μ, mu opioid; δ, delta opioid; κ, kappa opioid.

* Tel.: +1 410 550 1634; fax: +1 410 550 5172, +1 410 550 1612.
E-mail address: egardner@intra.nida.nih.gov.

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1. Introduction

The brain's reward circuitry consists of synaptically interconnected neurons which link the ventral tegmental area (VTA), medial forebrain bundle (MFB), nucleus accumbens (Acb) (and closely-related structures ventral to the Acb, including the olfactory tubercle), ventral pallidum (VP), and medial prefrontal cortex (MPFC). Laboratory rodents, canines, and non-human primates avidly self-administer mild electrical stimulation to these loci, which is also reported by humans to be intensely pleasurable. This core reward circuitry is strongly implicated in the neural processes underlying drug addiction. Activation of this circuit correlates with drug-seeking and drug-taking behaviors. Inhibition of this circuit is implicated in withdrawal dysphoria and dysphoria-mediated drug craving. These brain mechanisms are believed to have evolved to subserve biologically essential natural rewards. Although considered for years to lack action on this core reward circuitry, cannabinoids (which have euphorigenic and addictive potential in humans) are now known to interact with these brain mechanisms and influence drug-seeking and drug-taking behaviors in a manner strikingly similar to that of other reward-enhancing drugs. At the same time, very recent advances in understanding the endogenous cannabinoid system(s) of the brain make it increasingly likely that while cannabinoids activate the reward pathways in a manner consistent with other reward-enhancing drugs, the cellular mechanisms through which this occurs may well differ.

2. Loci and mechanisms of brain reward

2.1. Neuroanatomical, neurophysiological, and neurochemical substrates of brain reward

The neuroanatomical, neurophysiological, and neurochemical substrates of brain reward involve neural loci and mechanisms associated with the MFB, located primarily in the ventral limbic midbrain/forebrain (Gardner, 1997). Wise and Bozarth (1984) were the first to formally suggest that these reward substrates consist of "first-stage," "second-stage," and "third-stage" reward-related neurons "in series" with one another, a suggestion corroborated by subsequent work (for review, see Gardner, 1997). Anatomical and electrophysiological studies (e.g.,

Gallistel et al., 1981) have shown that the "first-stage" neurons originate from ventral limbic forebrain loci anterior to the hypothalamus. These "first-stage" neurons are the ones directly activated by rewarding electrical brain stimulation. These neurons (of unknown neurotransmitter type) project posteriorly through the MFB to synapse on VTA DA cells. These "second-stage" DA neurons project anteriorly through the MFB to synapse in the Acb. From Acb, "third-stage" neurons carry the reward signal onward to VP and other loci important for the expression of reward-related and incentive-related behaviors (Bardo, 1998; Napier and Mitrovic, 1999; McBride et al., 1999). Some of these "third-stage" neurons utilize the neurotransmitter γ-aminobutyric acid (GABA), and GABAergic medium spiny Acb output neurons are implicated in brain reward functions (Carlezon and Wise, 1996a). This core brain reward system receives extensive additional neural input from numerous modulatory systems—including opioidergic, serotonergic, GABAergic, and glutamatergic (Gardner, 1997). The GABAergic and glutamatergic neural inputs appear especially important to the regulation of reward processes and reward-driven behaviors (Gardner, 2000; Vorel et al., 2001). From single-neuron electrophysiological recording studies (e.g., Schultz et al., 1997; Redgrave et al., 1999; Woodward et al., 1999), the argument has been made that the core brain reward system may encode a great deal more than simple hedonic tone. In fact, it has been argued that the encoding of hedonic tone per se may be less important than the encoding of reward expectancy, disconfirmation of reward expectancy, prioritized reward, and other more complex aspects of reward-driven learning and reward-related incentive motivation (Gardner and Lowinson, 1993; Di Chiara, 1995; Wickelgren, 1997; Berridge and Robinson, 1998; Everitt et al., 1999). However, others have argued compellingly that, even if other reward-related functions are mediated by the core VTA–MFB–Acb reward system, one of the primary functions of this system is to compute hedonic tone and neural "payoffs" (Kornetsky and Bain, 1992; Kornetsky and Duvauchelle, 1994; Shizgal, 1997; Peoples et al., 1999). As noted by Goldstein (2001), these brain reward mechanisms presumably evolved to subserve natural, biologically significant rewards, and their activation by addictive drugs constitutes a form of pharmacological "hijacking" of normal brain reward functions.

2.2. Brain reward mechanisms as affected by addictive drugs

Addictive drugs activate the core brain reward system, primarily by activating the "second-stage" DA neurons of the VTA–Acb axis, thus producing the pleasurable/euphoric effects that constitute the "high" or "blast" (Simon and Burns, 1997) sought by drug addicts. Some addictive drugs such as amphetamines or cocaine activate these reward mechanisms directly, at the DA terminal loci in the Acb. Other addictive drugs such as opiates activate these reward mechanisms neurons indirectly (Gardner, 1997). Pharmacologically induced reward and drug potentiation of electrical brain-stimulation reward (BSR) appear to have common actions within these reward substrates (Wise, 1996). The key to the reward-enhancing power of addictive drugs is that pharmacologically induced reward is more powerful and immediate than the reward produced by natural, biologically essential reinforcers (Goldstein, 2001). It is in this context that addictive drugs may be said, as noted above, to "hijack" these reward substrates.

2.3. Dysregulation of brain reward substrates as a cause of addiction

The question arises—why can some people use addictive drugs on an occasional non-addictive basis (e.g., the occasional glass of wine with dinner), while others deteriorate into a self-destructive, addictive pattern of use (e.g., the repeated, obsessional, compulsive pattern of use seen in those meeting diagnostic criteria for alcoholism)? Genetic factors play an important role, perhaps accounting for as much as 50% of the variance in people with clinically defined alcohol or drug addiction (Uhl et al., 1993). The importance of genetic factors at the animal level, both in terms of drug-taking behavior and the ease with which environmental cues acquire positive incentive salience from being paired with addictive drugs, is also clear (George and Goldberg, 1989; Suzuki et al., 1989; Guitart et al., 1992; Kosten et al., 1994). These genetic vulnerability factors may, in turn, produce deficiency states in DA function within VTA–Acb DA reward-related neurons. It has been reported (e.g., Beitner-Johnson et al., 1991; Guitart et al., 1992, 1993; Nestler, 1993; Kosten et al., 1994, 1997; Self and Nestler, 1995) that, in laboratory animals, genetic vulnerability to drug-seeking and drug-taking behavior correlates with a DA deficiency at the MFB–Acb interface in the reward system, as a result of cellular changes in the "second-stage" DA reward-related neurons (see Gardner, 1999, for review). Another hypothesis involving "functional" DA deficiency in the VTA–Acb brain reward axis focuses on a deficiency in DA receptors rather than in DA itself. Blum and colleagues have long hypothesized that a deficit in normal DA D2 receptor function in meso-accumbens brain reward loci may confer vulnerability to drug addiction (e.g., Blum et al., 1996a,b). Recently, this hypothesis has received support from human neuroimaging findings of diminished DA D2 receptor levels in brain reward loci of drug addicts (Volkow et al., 1996, 1997, 2001), from findings that low levels of DA D2 receptors in human brain reward loci predict rewarding versus non-rewarding subjective responses to psychostimulants (Volkow et al., 1999), and from animal studies in which overexpression of DA

D2 receptors decreases drug-seeking and drug-taking (e.g., Thanos et al., 2001). A more complex explanatory scheme of the neurobiological processes underlying both initial vulnerability and relapse to drug addiction–involving a cascade of homeostatic dysregulations within both the brain's VTA–MFB–Acb reward substrates and in circuits interconnecting with these reward substrates–has been proposed by Koob and Le Moal (1997) and Koob (1999). In this view, vulnerability to drug abuse conferred by genetic factors, drug use, or withdrawal dysphoria is conceived to involve decreased VTA–MFB–Acb reward function coupled with increases in the brain-stress neurotransmitter corticotropin releasing factor (CRF) in the central nucleus of the amygdala (CeA). In this view, it is the combination of decreased positive drug-induced reward, increased opponent neural processes within reward loci, and recruitment of brain-stress neural systems within the extended amygdala which provides the allostatic change in overall hedonic set point that leads to the compulsive drug-seeking and drug-taking that characterizes drug abuse (Koob et al., 1993; Koob and Le Moal, 1997; Koob, 1999).

3. Reward-related behaviors

3.1. Using animal behaviors to model addiction

Addictive behavior at the human level can be successfully modeled at the animal level, with seemingly good face validity to the human situation (Gardner, 2000; Wise and Gardner, 2004). These models include conditioned place preference, drug self-administration, and reinstatement.

3.1.1. Conditioned place preference

Conditioned place preference (CPP) was developed to study *drug-seeking* behavior at the laboratory animal level, and–from that–to infer incentive motivational value of addictive drugs (Mucha et al., 1982; van der Kooy, 1987; Schechter and Calcagnetti, 1993; Tzschentke, 1998). The CPP procedure is based upon the ability of neutral environmental cues or contexts to acquire incentive salience (Bindra, 1968; Robinson and Berridge, 1993) by being paired with the subjective state produced by addictive drugs. Important for present purposes, CPP is DA dependent (Wise and Gardner, 2002, 2004).

3.1.2. Drug self-administration

The drug self-administration paradigm is used to study *drug-taking* behavior, and offers the most obvious animal model of addiction—all the more so because laboratory animals self-administer addictive drugs in the absence of physical dependence (Bozarth and Wise, 1984; Gardner, 1997, 2000). An especially informative version of this model is that in which progressive ratio (PR) reinforcement is used (Richardson and Roberts, 1996). In PR drug self-administration, a progressively increasing work-load is imposed on the animal (in order to receive the next drug injection) until the animal's responding falls off (usually abruptly)—the so-called PR "break-point." This "break-point" is taken as a measure of the drug's rewarding efficacy, and parallels human verbal reports of drug "appeal" (Gardner, 2000). Important for present purposes, drug self-administration in laboratory animals is DA dependent (Gardner, 2000; Wise and Gardner, 2002, 2004).

3.1.3. Reinstatement

The "reinstatement" paradigm allows *relapse* to drug-seeking and drug-taking behavior to be studied. In this paradigm animals are trained to self-administer, then subjected to extinction of the drug-taking habit (by withholding the drug reward), and then various stimuli are used to provoke relapse to the extinguished drug-seeking behavior. Three types of stimuli provoke relapse in this model—a single non-contingent "priming" administration of drug (de Wit and Stewart, 1981, 1983; Stewart, 1984; Stewart and de Wit, 1987), stress (Shaham and Stewart, 1995; Erb et al., 1996; Shaham et al., 1996), or environmental cues previously associated with the drug-taking habit (Meil and See, 1996; McFarland and Ettenberg, 1997; Katner et al., 1999). These are the same stimuli that provoke relapse to drug-taking at the human level (Gardner, 2000). The Acb and the neurotransmitter DA are essential for drug-triggered reinstatement (Grimm and See, 2000; Shalev et al., 2002). The basolateral amygdala (BLA) and the neurotransmitter glutamate are essential for cue-triggered reinstatement (Grimm and See, 2000; Hayes et al., 2003). The CeA, bed nucleus of stria terminalis (BNST), lateral tegmental noradrenergic projection system, and the CRF projection pathway from the CeA to the BNST are essential for stress-triggered reinstatement (Shalev et al., 2002). Important for present purposes, the drugs and doses which "prime" relapse to drug-seeking in humans and animals are drugs and doses which *increase* DA function within the core VTA–MFB–Acb DA reward system (Stewart and Vezina, 1988; Wise et al., 1990).

3.2. Reward-related behaviors as "probes" of addictive drug action

Very few drugs support drug-seeking and drug-taking at the laboratory animal level (Griffiths et al., 1978; Brady and Lucas, 1984; Yokel, 1987). It is in this context that the reward-related behaviors cited above become important to understanding brain reward substrates and mechanisms. With few exceptions, addictive drugs support CPP (Mucha et al., 1982; Schechter and Calcagnetti, 1993; Tzschentke, 1998; Wise and Gardner, 2004). With few exceptions, addictive drugs support voluntary self-administration by laboratory animals (and drugs that are *dysphorigenic* in

humans are *negative* reinforcers in laboratory animals) (Griffiths et al., 1978; Brady and Lucas, 1984; Amit et al., 1987; Brady et al., 1987; Meisch and Carroll, 1987; Weeks and Collins, 1987; Yanagita, 1987; Yokel, 1987; Gardner, 1997, 2000; Wise and Gardner, 2004). With few exceptions, addictive drugs "prime" or trigger relapse to drug-seeking behavior (de Wit and Stewart, 1981, 1983; Stewart, 1984; Stewart and de Wit, 1987; Stewart and Vezina, 1988; Wise et al., 1990; Shaham et al., 1996; Gardner, 2000; Shalev et al., 2002; Wise and Gardner, 2004). Thus, CPP, self-administration, and reinstatement can be used as behavioral indices of central reward processes.

4. Cannabinoid and endocannabinoid brain substrates

4.1. Cannabinoid receptors in the brain

The prototypical psychoactive cannabinoid–Δ^9-tetrahydrocannabinol (THC)–was isolated and identified from marijuana and hashish in the 1960s (Gaoni and Mechoulam, 1964). The binding site in the brain at which THC acts was cloned, identified, and designated as the CB1 receptor in the 1990s (Matsuda et al., 1990). The CB1 receptor, found in brain, and the subsequently identified CB2 receptor, found in peripheral tissues, are both coupled to inhibitory G_i/G_o proteins (for review see Pertwee, 1997). At present, there is evidence for at least one additional novel cannabinoid receptor in the brain (Breivogel et al., 2001), and quite possibly even more new cannabinoid receptors (Hajos et al., 2001; Hajos and Freund, 2002). The CB1 receptor is found widely throughout the brain (Herkenham et al., 1990, 1991; Hohmann and Herkenham, 2000).

4.2. Second-messenger transduction mechanisms activated in brain by cannabinoids

The CB1 receptor is linked to a surprisingly large number of second messenger transduction mechanisms in the brain. The CB1 receptor activates potassium channels and MAP kinase, and inhibits adenylyl cyclase and voltage-dependent calcium channels (Bidaut-Russell et al., 1990; Henry and Chavkin, 1995; Twitchell et al., 1997; Hoffman and Lupica, 2000). It has only recently become evident that the CB1 receptor, by activating or inhibiting these various membrane-associated transduction mechanisms, may well play an important regulatory role, especially on glutamatergic and GABAergic neurons, in the core VTA–MFB–Acb reward axis (see below for further explication).

4.3. Endogenous cannabinoid neurotransmitters/neuromodulators (endocannabinoids)

As was the case when the initial discovery of opioid receptors in the brain (μ, δ, κ, etc.) was soon followed by the discovery of endogenous neurotransmitters/neuromodulators acting upon those receptors (endorphins, enkephalins, dynorphins, etc.), so too has a similar path of discovery uncovered endogenous neurotransmitters/modulators that act as natural ligands at cannabinoid receptors in the brain. The first to be discovered was anandamide (named by its discoverer for the Sanskrit word meaning "bliss"), followed by 2-arachidonylglycerol (2-AG) (for review, see Mechoulam et al., 1998). This is currently a very active area of research, with very real prospects for the identification of additional endocannabinoids functioning as synaptic messengers.

4.4. Endocannabinoid synaptic function

Remarkably, endocannabinoids appear to act as *retrograde* neurotransmitters—released from postsynaptic neurons upon membrane depolarization, migrating in retrograde fashion to an adjacent presynaptic membrane, activating presynaptic CB1 receptors, and inhibiting neurotransmitter release presynaptically (Alger, 2002; Wilson and Nicoll, 2002). This retrograde neurotransmitter function of endocannabinoids has been identified in both the VTA and Acb of the brain's core reward-related neural axis (Robbe et al., 2002; Melis et al., 2004), a point we shall return to.

5. Brain reward substrates are pharmacologically activated by cannabinoids

Although denied by some (e.g., Felder and Glass, 1998), the evidence that cannabinoids have addictive potential is impressive (Kozel and Adams, 1986; Kleber, 1988; Goldstein and Kalant, 1990; Anthony et al., 1994; Hall et al., 1994; MacCoun and Reuter, 1997; Crowley et al., 1998). The question arises—do cannabinoids derive their addictive potential by activating the core VTA–MFB–Acb reward system, or by other neuropharmacological actions? Evidence from a number of reward-related paradigms speaks to this question.

5.1. Cannabinoids enhance electrical brain-stimulation reward (BSR)

THC at low and pharmacologically meaningful doses (e.g., 1.0 mg/kg) enhances electrical BSR (i.e., lowers brain reward thresholds) in the VTA–MFB–Acb reward axis in laboratory animals (Gardner et al., 1988a; Gardner and Lowinson, 1991; Gardner, 1992; Lepore et al., 1996). This enhancement of brain reward has been reported from experiments in which two very different quantitative electrophysiological reward-threshold measurement techniques were applied, the auto-titration threshold measurement technique and the rate-frequency curve-shift threshold measurement technique. This congruence of findings using two different techniques adds credence to the reports.

5.2. Cannabinoids enhance DA neuronal firing in the VTA–MFB–Acb reward axis

In vivo single-neuron electrophysiological recording has been used to determine whether cannabinoids augment DA function in the VTA–MFB–Acb reward system by enhancing DA neuronal firing per se, as do nicotine and opioids (Gysling and Wang, 1983; Grenhoff et al., 1986; Gardner, 1997), or by enhancing DA release or inhibiting DA reuptake at the Acb DA terminals, as do cocaine and amphetamines (for review, see Gardner, 1997). The weight of the evidence is that THC and the potent synthetic cannabinoids WIN-55212-2 and CP-55940 enhance neuronal firing of DA neurons in forebrain reward loci (Melis et al., 1996; French, 1997; French et al., 1997; Diana et al., 1998a; Gessa et al., 1998; but see Gifford et al., 1997). This effect is also seen in other DA neural systems, but is more pronounced in the VTA–MFB–Acb DA reward axis than in other DA systems (French et al., 1997). This is congruent with the known preferential action of other addictive drugs on DA neurons of the VTA–MFB–Acb axis (Di Chiara, 1995; Pontieri et al., 1995; Di Chiara and Imperato, 1986; Gardner, 1997). The effect is blocked by the selective CB1 cannabinoid receptor antagonist SR-141716A (French, 1997; French et al., 1997; Diana et al., 1998a), but not by the opiate antagonist naloxone (French, 1997). This observation is relevant, because naloxone *does* attenuate cannabinoid-induced elevations of Acb DA (see below), and shall be returned to. Cannabinoids also enhance neuronal *burst* firing (Diana et al., 1998a), a neuronal firing pattern that produces supra-additive DA release at Acb axon terminals (Gonon, 1988; Overton and Clark, 1997).

5.3. Cannabinoids enhance synaptic DA in the VTA–MFB–Acb reward axis

5.3.1. In vitro assays

As studied by in vitro assays, THC enhances DA synthesis (Bloom, 1982; Navarro et al., 1993) and inhibits DA neuronal reuptake (Banerjee et al., 1975; Johnson et al., 1976; Hershkowitz et al., 1977; Poddar and Dewey, 1980), as do other cannabinoids (Bloom et al., 1977). With respect to cannabinoid effects on DA release, as studied by in vitro assays, the picture is unclear. Enhancement (Poddar and Dewey, 1980; Jentsch et al., 1998), no effect (Szabo et al., 1999), and inhibition (Cadogan et al., 1997) of DA release by cannabinoids have all been reported.

5.3.2. In vivo assays

Using in vivo brain microdialysis in awake animals, Gardner and colleagues were the first to report that cannabinoids enhance extracellular DA overflow in brain reward axon terminal loci (Ng Cheong Ton and Gardner, 1986, Ng Cheong Ton et al., 1988; Chen et al., 1989, 1990a,b). Subsequent work was confirmatory (e.g., Taylor et al., 1988; Tanda et al., 1997; Malone and Taylor, 1999; but see Castañeda et al., 1991). This DA-enhancing effect is tetrodotoxin-sensitive, calcium-dependent, and naloxone-blockable (Chen et al., 1990b; Gardner et al., 1990a; Gardner and Lowinson, 1991; Gardner, 1992; Tanda et al., 1997), is blocked by the CB1 antagonist SR-141716A, and is also produced by the potent synthetic cannabinoid WIN-55212-2 (Tanda et al., 1997). THC's DA-enhancing effect is anatomically selective to the Acb "shell" subdivision (Tanda et al., 1997), which is congruent with a large body of evidence identifying the shell subdivision as mediating drug-enhanced brain reward (Johnson et al., 1995; Pontieri et al., 1995; Carlezon and Wise, 1996a; Gardner, 1997; McBride et al., 1999). Gardner and colleagues were also the first to report that cannabinoids enhance extracellular DA overflow as measured by in vivo voltammetry (Ng Cheong Ton et al., 1988; Gardner and Lowinson, 1991). At this point, the issue is beyond dispute.

5.4. Cannabinoid action on brain reward substrates is genetically variable

An interesting feature of addictive drug action is that the behavioral phenotypes of "drug-seeking" and "drug-taking" are subject to a high degree of genetic variation (George and Meisch, 1984; Khodzhagel'diev, 1986; Cannon and Carrell, 1987; George, 1987; George and Goldberg, 1989; Suzuki et al., 1989; Guitart et al., 1992; Nestler, 1993; Kosten et al., 1994, 1997). The Lewis rat strain has been particularly useful as a laboratory model of this variability, as they are inherently drug-seeking and drug-preferring (George and Goldberg, 1989; Suzuki et al., 1989; Guitart et al., 1992; Nestler, 1993; Kosten et al., 1994, 1997). The question arises—do cannabinoid effects on brain reward processes mimic the genetic variations shown by other addictive drugs? The answer appears to be "yes". Using quantitative electrophysiological BSR techniques, THC has been found to produce robust BSR enhancement in the drug-preferring Lewis rat strain, moderate enhancement in the drug-neutral Sprague–Dawley strain, and no change in the drug-resistant Fischer 344 strain (Gardner et al., 1988b, 1989a; Lepore et al., 1996). Using in vivo brain microdialysis, THC has been found to produce robust enhancement of Acb DA in the drug-preferring Lewis rat strain, moderate enhancement in the drug-neutral Sprague–Dawley strain, and no change in the drug-resistant Fischer 344 strain (Gardner et al., 1989a; Chen et al., 1991).

5.5. Cannabinoid withdrawal and brain reward substrates

As noted above, enhancement of BSR and DA in brain reward loci are distinct neuropharmacological "signatures" of addictive drugs. Conversely, *withdrawal* from addictive drugs produces *inhibition* of BSR and DA in the VTA–MFB–Acb brain reward axis (Schaefer and Michael, 1986; Frank et al., 1988; Parsons et al., 1991; Pothos et al., 1991; Rossetti et al., 1992; Schulteis et al., 1994; Wise and Munn,

1995)—equally distinct neuropharmacological "signatures" of addictive drugs. The question arises—does cannabinoid withdrawal mimic withdrawal from other addicting drugs with respect to these two additional neuropharmacological "signatures"? The answer is "yes". Withdrawal from as little as a single 1.0 mg/kg dose of THC produces significant inhibition of BSR (Gardner and Vorel, 1998), of neuronal cell firing (Diana et al., 1998b), and of Acb shell DA (Tanda et al., 1999)—all in the core VTA–MFB–Acb reward axis. Another distinguishing "signature" of addictive drugs is CRF elevation in the CeA during drug withdrawal (Koob et al., 1993; Merlo Pich et al., 1995; Koob, 1996). This is provocative, as the amygdala appears to mediate an emotional memory system that facilitates drug-seeking behavior (Cador et al., 1989; Everitt et al., 1989, 1999; Hiroi and White, 1991; Gaffan, 1992; White and Hiroi, 1993; Hayes et al., 2003). The question arises—does cannabinoid withdrawal mimic withdrawal from other addictive drugs in this regard? The answer is "yes". Significant elevation of extracellular CeA CRF is seen during cannabinoid withdrawal (Rodríguez de Fonseca et al., 1997). Thus, cannabinoid withdrawal mimics withdrawal from other addictive drugs with respect to effects in the two main brain loci mediating drug-taking, drug-seeking, and relapse—the core VTA–MFB–Acb brain reward axis and the amygdala (Koob, 1999).

5.6. Cannabinoid actions on brain reward substrates are mediated by an endogenous opioid peptide mechanism

As noted above, the core VTA–MFB–Acb brain reward axis is anatomically interconnected with endogenous brain opioid peptide systems, which exert a modulatory influence on it (Gardner, 1997, 2000). This is the substrate of yet another distinguishing "signature" of addictive drugs—the fact that the enhanced brain reward produced by addictive drugs (including non-opiates, e.g., ethanol, barbiturates, cocaine) is blocked or attenuated by opiate antagonists (Gardner, 1997). The question arises—are cannabinoid effects on brain reward systems similarly blocked or attenuated by opiate antagonists? The answer is "yes". Using quantitative electrophysiological BSR measurements, the opiate antagonist naloxone attenuates THC-induced enhancement of BSR (Gardner et al., 1989b; Gardner and Lowinson, 1991; Gardner, 1992). Using in vivo brain microdialysis measurements, the opiate antagonist naloxone attenuates THC-induced enhancement of Acb DA (Chen et al., 1989, 1990b; Gardner et al., 1989b, 1990a; Gardner and Lowinson, 1991; Gardner, 1992; Tanda et al., 1997). The selective μ_1 opiate antagonist naloxonazine does also (Tanda et al., 1997). These findings using in vivo brain microdialysis are congruent with older in vitro biochemical data that naloxone attenuates THC-enhanced DA synthesis (Bloom and Dewey, 1978). In the self-administration behavioral assay, opioid antagonism significantly attenuates THC self-administration (Braida et al., 2001b; Justinova et al., 2004; see also below). Provocatively, cannabinoid and opioid receptors are coupled to similar postsynaptic transduction mechanisms—activation of G_i proteins, inhibition of adenylyl cyclase, and decreased cAMP production (Childers et al., 1992). As CB1 cannabinoid receptors are co-localized with μ opioid receptors in the Acb (Navarro et al., 1998), it has been suggested that cannabinoids and opioids may interact at the level of these postsynaptic transduction mechanisms (Thorat and Bhargava, 1994). Additional interaction may take place at the receptor level, as brain opioid receptors are modulated by cannabinoids (Vaysse et al., 1987) and brain cannabinoid receptors are modulated by opiates (Rubino et al., 1997). A peculiarity is that while opiate antagonism attenuates cannabinoid enhancement of BSR and Acb DA (see above for references), and attenuates cannabinoid self-administration (see further mention below), it does *not* alter cannabinoid enhancement of the firing rates of VTA–MFB–Acb DA neurons (French, 1997; Gessa and Diana, 2000). We shall return to this point, and its possible implications for underlying neural mechanisms.

6. Reward-related behaviors are pharmacologically activated by cannabinoids

As noted above, certain characteristic animal behaviors are evoked rather uniquely by addictive drugs and can thus be used as pharmaco-behavioral "signatures" of addictive drug action. As noted, such "signature" behaviors of addictive drug action include enhancement of CPP, self-administration, and the triggering of relapse (reinstatement) to drug-seeking behavior in animals extinguished from the drug-taking habit. The question arises—do cannabinoids support CPP, self-administration, and reinstatement? The answer appears to be "yes".

6.1. Cannabinoids produce CPP

Although some workers have reported that cannabinoids produce conditioned place *aversion* (CPA) (Parker and Gillies, 1995; McGregor et al., 1996; Sañudo-Peña et al., 1997; Chaperon et al., 1998; Hutcheson et al., 1998; Mallet and Beninger, 1998; Cheer et al., 2000a), three research groups have independently reported robust cannabinoid-induced CPP (Lepore et al., 1995; Valjent and Maldonado, 2000; Braida et al., 2001a). The crucial differences appear to be cannabinoid dose (Lepore et al., 1995), timing (Lepore et al., 1995; Valjent and Maldonado, 2000), and potency (Braida et al., 2001a). When the CPP pairing interval was 24 h (within the post-cannabinoid dysphoric rebound—see above section on cannabinoid withdrawal), Lepore et al. (1995) found that 1.0 mg/kg THC produced no CPP, while 2.0 or 4.0 mg/kg produced robust CPP. When the CPP pairing interval was 48 h (past

the post-drug dysphoric rebound) 1.0 mg/kg THC produced robust CPP, while 2.0 or 4.0 mg/kg produced CPA. The interpretation is that at the shorter pairing interval the post-cannabinoid rebound dysphoria attenuated THC's rewarding effect, eliminating the reward of the 1.0 mg/kg dose and lowering the 2.0 and 4.0 mg/kg doses into the rewarding range. At the longer pairing interval, the post-cannabinoid dysphoric rebound had passed, accentuating the effects of all doses—allowing the 1.0 mg/kg dose to become rewarding, and pushing the 2.0 and 4.0 mg/kg doses up into an aversive dose range. Such dose-dependent switches from reward to aversion (low dose-reward; high dose-aversion) have also been seen with other addictive drugs (Fudala et al., 1985; Jorenby et al., 1990; Gardner, 1992). A parallel phenomenon exists at the human level—low-to-moderate THC doses produce reward but higher doses produce aversion (Noyes et al., 1975; Raft et al., 1977; Laszlo et al., 1981). Also, timing of drug administration during place conditioning is as strong a determinant of CPP or CPA as the drug itself (Fudala and Iwamoto, 1990), and this appears so with cannabinoid-induced CPP (Valjent and Maldonado, 2000). When a long conditioning period was used and care taken to avoid dysphoric rebound from prior THC administrations, THC produced a robust CPP (Valjent and Maldonado, 2000). Also, the potent synthetic cannabinoid CP-55940 produced a robust CPP (Braida et al., 2001a). Notably, given the attenuation of cannabinoid-induced effects in other reward paradigms by opiate antagonists, CP-55940's induction of CPP was fully antagonized by naloxone (Braida et al., 2001a).

Thus, under proper experimental circumstances, cannabinoids *do* produce rewarding effects in the CPP paradigm, a behavioral "signature" of addictive drugs. This rewarding effect of cannabinoids is attenuated by opiate antagonists, another distinctive "signature" of addictive drugs.

6.2. Cannabinoids are self-administered

The older animal behavioral literature on cannabinoid self-administration was mixed, with some reports (dubious on methodological grounds) of success (e.g., Deneau and Kaymakçalan, 1971; Kaymakçalan, 1972; Pickens et al., 1973; Takahashi and Singer, 1979, 1980), and many reports of failure (e.g., Kaymakçalan, 1972, 1973; Corcoran and Amit, 1974; Leite and Carlini, 1974; Harris et al., 1974; Carney et al., 1977; Takahashi and Singer, 1981; Mansbach et al., 1994). Recently, however, several groups have independently reported cannabinoid self-administration in laboratory animals under methodologically clean conditions. The potent synthetic cannabinoid agonist WIN-55212-2 is intravenously self-administered by drug-naive mice (Fratta et al., 1997; Martellotta et al., 1998; Ledent et al., 1999), the self-administration being blocked by the selective CB1 antagonist SR-141716A. The potent synthetic cannabinoid agonist CP-55940 is also self-administered by laboratory rats (by the intracerebroventricular route) (Braida et al., 2001b), again being blocked by SR-141716A. Notably, in view of the involvement of endogenous opioid mechanisms in mediating reward-related behaviors, the cannabinoid self-administration was blocked by the opiate antagonist naloxone (Braida et al., 2001b). Low-dose intravenous THC is robustly self-administered by squirrel monkeys (Tanda et al., 2000; Justinova et al., 2003), and this self-administration is blocked by *either* the CB1 antagonist SR-141716A (Tanda et al., 2000) *or* the opiate antagonist naltrexone (Justinova et al., 2004). The THC doses which supported self-administration in these studies are comparable to doses found in marijuana smoke inhaled by human users (Tanda et al., 2000; Justinova et al., 2003), and are from 5000 to 25,000-fold lower than the doses required to induce cannabinoid physical dependence in rats or mice (Tsou et al., 1995; Aceto et al., 1996, 2001; Hutcheson et al., 1998; Cook et al., 1998; Ledent et al., 1999; Tzavara et al., 2000).

6.3. Cannabinoids and reinstatement

As noted above, the reinstatement model of relapse to drug-seeking behavior is an animal behavioral model which also reveals a characteristic "signature" of addictive drugs. Relapse to drug-seeking behavior in the reinstatement model is characteristically "primed" or triggered by drugs with addictive properties. The relatively small amount of work which has been done with cannabinoids in this model reveals that cannabinoids fit the same pattern as other addictive drugs. The synthetic cannabinoid receptor agonist HU-210 dose-dependently reinstates cocaine-seeking and heroin-seeking behavior in laboratory rats behaviorally extinguished from intravenous drug self-administration (De Vries et al., 2001). The CB1 receptor antagonist SR-141716A *blocks* reinstatement to drug-seeking behavior triggered by cocaine, heroin, or cocaine-associated environmental cues in this model (De Vries et al., 2001), but not relapse induced by exposure to stress, suggesting a role for *endocannabinoid* mechanisms in the neurobiological substrates of addiction.

7. Cannabinoid enhancement of reward—possible modulation of VTA–MFB–Acb DA-dependent substrates at the level of the VTA

As noted above, a major puzzle exists with respect to endogenous opioid substrates involved in cannabinoid enhancement of brain reward mechanisms. Opiate antagonists attenuate cannabinoid-induced enhancement of BSR (Gardner et al., 1989b; Gardner and Lowinson, 1991; Gardner, 1992), cannabinoid-induced enhancement of Acb DA (Chen et al., 1989, 1990b; Gardner et al., 1989b, 1990a; Gardner and Lowinson, 1991; Gardner, 1992; Tanda et al., 1997), and cannabinoid self-administration by laboratory

rodents and monkeys (Braida et al., 2001b; Justinova et al., 2004). Yet, opiate antagonists do *not* alter cannabinoid enhancement of the firing rates of VTA–MFB–Acb DA neurons (French, 1997; Gessa and Diana, 2000). The question arises—what mechanisms within the core VTA–MFB–Acb reward axis can be suggested that might help explain this seeming conundrum?

As also noted above, opiates act within the VTA to disinhibit DA neuronal activity, leading to enhancement of DA neural firing and consequent enhancement of Acb DA. Could cannabinoids do the same? Single-neuron electrophysiological recording studies have indeed shown that THC and other potent CB1 receptor agonists (e.g., WIN-55212-2, CP-55940, HU-210) enhance neuronal firing rates in the VTA, both in intact animals (French et al., 1997; Gessa et al., 1998; Wu and French, 2000) and also in brain slices containing the VTA (Cheer et al., 2000b). Importantly, the cannabinoid-induced enhancement of DA neuronal firing was accompanied by increased DA neuronal burst firing (French et al., 1997; Diana et al., 1998a), which is important because (as noted above) DA neuronal burst-pattern firing produces dramatically augmented terminal axonal DA release (Gonon, 1988). Of equal importance in these experiments, the cannabinoid-induced enhancements in DA neuronal firing were attenuated by the CB1 antagonist SR-141716A, clearly implicating an endocannabinoid mechanistic substrate. The straightforward interpretation of such findings is that cannabinoid-induced enhancement of the VTA–MFB–Acb DA core reward axis (which then leads to, e.g., enhanced extracellular Acb DA) results from cannabinoid-induced enhancement of DA neuronal firing and burst firing of VTA DA neurons. Further, the fact that the CB1 agonist HU-210 increases the activity of VTA DA neurons *in brain slice preparations* is strongly suggestive of two alternative possibilities. First, that cannabinoids may act on the VTA DA neurons themselves. Second, that cannabinoids may act on local circuits within the VTA to enhance DA neuronal firing and bursting.

7.1. Cannabinoid action directly on VTA DA neurons

It was originally believed that CB1-mediated direct action of cannabinoid agonists on VTA DA neurons was not possible, in view of the inability of early studies to find CB1 receptors on those DA neurons (Herkenham et al., 1990, 1991). However, more recent reports reveal co-localization of immunoreactivity for the CB1 receptor and for tyrosine hydroxylase (synthesizing enzyme for DA, a commonly used cellular marker for the presence of DA neurons) *in the VTA* (Wenger et al., 2003). This means that direct action of cannabinoid agonists on DA cells in the VTA appears to be anatomically and morphologically possible.

Supporting functional evidence comes from studies in which local microinjections of cannabinoids have been made directly into the VTA and local VTA extracellular DA overflow measured by in vivo brain microdialysis (Chen et al., 1993). In those studies, THC microinfusions into the VTA dose-dependently enhanced local DA within the VTA. This suggests that cannabinoid-enhanced brain reward functions and reward-related behaviors driven by substrates and mechanisms within the VTA could be due to direct local cannabinoid actions on DA neurons within the VTA.

7.2. Cannabinoid action on local VTA circuits to indirectly enhance DA neurons

In the slice preparation work alluded to above (Cheer et al., 2000a,b), it was found that the excitatory actions on VTA DA neurons of the potent cannabinoid agonist HU-210 were blocked by prior application of the $GABA_A$ receptor antagonist bicuculline. This is an important observation, as it suggests that CB1 receptors may increase local VTA DA neuronal activity by means of local disinhibitory mechanisms involving GABAergic substrates in the VTA—similar to the manner in which opioids act within the VTA to enhance VTA–MFB–Acb reward functions (e.g., Johnson and North, 1992). This possibility gains further credence from recent experiments showing that local application of the cannabinoid WIN-55212-2 in brain slices containing the VTA *attenuates* electrically evoked *inhibitory* postsynaptic currents mediated by $GABA_A$ receptors (Szabo et al., 2002). Additionally, this effect seems to be mediated by CB1 receptors on *inhibitory GABAergic neurons within the VTA*, as it is blocked by application of SR-141716A and *not* seen following dendritic application of the $GABA_A$ *agonist* muscimol. Also, tetrodotoxin-resistant spontaneous inhibitory postsynaptic currents were unaffected by cannabinoid agonist application, suggesting that the GABAergic inhibitory postsynaptic currents were *not* altered at a postsynaptic *location* by the cannabinoid application. The implication is that the effect is mediated presynaptically. This is compelling, as presynaptic inhibition of neurotransmitter release is perhaps the most well-established action of CB1 receptor activation in the brain (Hoffman and Lupica, 2000, 2001). Furthermore, CB1 receptors are found prolifically on GABAergic terminals (e.g., Freund et al., 2003), positioning them well for the kind of disinhibitory mechanism proposed. An important caveat is in order, however. In the experiments by Szabo et al. (2002) cited above, the affected neurons were not satisfactorily characterized as DAergic. Thus, the disinhibitory scheme involving a $GABA_A$ substrate sketched out above, while attractive–especially in its parallel to opioid-activated mechanisms within the VTA–MFB–Acb reward substrates–is far from proven. Indeed, it is difficult to even posit a probability estimate for its accuracy. Adding additional complexity and difficulty for this model are recent experiments showing that cannabinoids and endocannabinoids, acting in retrograde fashion, inhibit glutamate release within the VTA (Melis et al.,

2004). Such release would therefore *attenuate* excitatory inputs to VTA DA neurons, reducing the probability of DA firing and burst firing (see, e.g., Kitai et al., 1999).

Adding additional complexity and interest for this model is the fact that additional CB1 receptors are located on axon terminals in the VTA which originate from GABAergic medium spiny output neurons in the Acb (Walaas and Fonnum, 1980; Heimer et al., 1991). Importantly, these Acb medium spiny GABAergic output neurons run caudally into the VTA where they synapse on $GABA_B$ receptors on DA neurons (Sugita et al., 1992). These additional CB1 receptors appear to inhibit $GABA_B$-mediated synaptic currents in the VTA (Riegel et al., 2003). The importance of this finding is great, because (when taken together with the previously noted work of Szabo et al., 2002) it suggests that cannabinoids may have a *dual* GABAergic inhibitory action in the VTA—inhibiting VTA GABAergic substrates derived from *both* intrinsic and extrinsic sources. The action on $GABA_B$ substrates is especially intriguing, in view of a now-extensive body of evidence implicating GABAergic substrates–*acting specifically via the* $GABA_B$ *receptor*–in the neurobiological mechanisms subserving addiction to heroin (Xi and Stein, 1999), nicotine (Dewey et al., 1999), and cocaine (Roberts et al., 1996; Dewey et al., 1998; Ashby et al., 1999) (for review, see Gardner, 2000). Furthermore, it is *activation* of the $GABA_B$ receptor that appears to have *anti*-addiction properties in animal models (Roberts et al., 1996; Dewey et al., 1998, 1999; Ashby et al., 1999; Xi and Stein, 1999), lending inferential support to models implicating CB1 receptor-mediated *inhibition* of $GABA_B$-mediated synaptic currents in pro-addiction mechanisms (Riegel et al., 2003).

In summary, the data and suggestions cited above make it likely that cannabinoids have multiple potential sites and mechanisms of action within the VTA, involving GABAergic disinhibition of VTA DA neurons, by which they can enhance VTA DA reward-related substrates. The fact that such disinhibition mechanistically parallels opiate action on DA substrates in the VTA has made these conceptions appealing to many. However appealing these models may be, though, it is crucial to keep aware of the major puzzle with which this section opened—namely, that while opiate antagonists attenuate cannabinoid-induced enhancement of BSR, cannabinoid-induced enhancement of Acb DA, and cannabinoid self-administration (see above for references), opiate antagonists do *not* alter cannabinoid enhancement of the firing rates of VTA–MFB–Acb DA neurons (see above for references). Two conclusions seem warranted. First, that while the action of cannabinoids on CB1 receptors in the VTA may account for some aspects of cannabinoid-enhanced brain-reward and reward-related behaviors, additional sites and mechanisms both within and without the VTA must be considered. Second, parallel or perhaps even redundant substrates and mechanisms that do not involve an opioid component must be equally considered.

8. Cannabinoid enhancement of reward—possible modulation of VTA–MFB–Acb DA-independent substrates at the level of the Acb

In the present author's opinion, many of the conceptual difficulties with the models cited in the previous section derive from an over-emphasis upon the VTA as the crucial site of action for the reward-enhancing properties of cannabinoids. In truth, there seems no reason for such over-emphasis. The ascending DA neural component of the VTA–MFB–Acb core reward axis is crucial to drug-enhanced reward and reward-related behaviors because of neural events that occur at the site to which those DA neurons project—the Acb (Wise and Gardner, 2002). It makes sense, then, to look to the Acb for both DA-independent (this section) and DA-dependent (next section) mechanisms that might help to explain cannabinoid enhancement of brain reward and reward-related behaviors.

In fact, several classes of addictive drugs have direct effects on synaptic events in the Acb (Wise and Gardner, 2002). Importantly, a number of such drugs (e.g., cocaine, opioids, phencyclidine) are self-administered by laboratory animals directly into the Acb (Carlezon and Wise, 1996a; McBride et al., 1999; Wise and Gardner, 2002) and, when exogenously microinjected into the Acb, enhance MFB electrical brain-stimulation reward (Carlezon and Wise, 1996b).

Provocatively, many of these addictive drugs inhibit GABAergic and glutamatergic neurotransmission in the Acb, by either pre- or post-synaptic mechanisms (Harvey and Lacey, 1997; Martin et al., 1997; Chieng and Williams, 1998; Nicola and Malenka, 1998). Even more provocatively, Hoffman and Lupica (2001) have shown that cannabinoid agonist administration inhibits GABA release onto Acb medium spiny projection neurons by means of activating CB1 receptors on inhibitory axon terminals, a very important finding independently confirmed by Manzoni and Bockaert (2001). Based upon these findings, and other considerations cited above, Lupica et al. (2004) have proposed that at least some of the reward-enhancing properties of cannabinoids are referable to *direct* action within the Acb, a suggestion previously made by Gardner and colleagues (e.g., Gardner, 1992; Gardner and Lowinson, 1991; Gardner and Vorel, 1998; Wise and Gardner, 2002). However, Lupica et al. (2004) present a very different–and in many ways, very attractive–model than that of Gardner and colleagues. They base their model on the hypothesis (made previously by Carlezon and Wise, 1996a; see also Wise and Gardner, 2002) that the *essential* reward-related neural event in the Acb is not the activation of the ascending MFB DA fibers, but rather the event immediately postsynaptic to that one, i.e., inhibition of the GABAergic medium spiny neurons of the Acb. Logically, if that neural event can be accomplished by means other than activation of the ascending DA component of the VTA–MFB–Acb system, the end

result should be identical—enhancement of reward and reward-related behaviors. Provocatively, the GABAergic medium spiny neurons of the Acb appear to receive GABAergic neural input from both intrinsic GABAergic interneurons (Koós and Tepper, 1999) and from recurrent axon collaterals of the GABAergic medium spiny neurons themselves (Plenz, 2003). No compelling data currently exist to identify which source of GABAergic inhibition in the Acb is inhibited by CB1 receptor activation. Equally, no compelling data currently exist to conclude, if both sources are inhibited by cannabinoids, whether the intrinsic and recurrent collateral GABAergic inhibitory substrates are equally inhibited by cannabinoids, or if one GABAergic Acb substrate is disproportionally affected by cannabinoid-induced inhibition.

Once again, cannabinoid actions on glutamatergic substrates in Acb add complexity to this model. Cannabinoid agonists inhibit glutamate release onto Acb medium spiny GABAergic neurons, through activation of CB1 receptors linked to voltage-dependent potassium channels in the glutamatergic axon terminals (Robbe et al., 2002). If the essential neural substrate of reward in the Acb is inhibition of the GABAergic medium spiny neurons (Carlezon and Wise, 1996a), these various cannabinoid-evoked Acb mechanisms may interact with each other to affect that reward substrate in a complex manner. Obviously, more work is needed to ascertain to what degree any of these conceptual models is correct.

9. Cannabinoid enhancement of reward—possible modulation of VTA–MFB–Acb DA-dependent substrates at the level of the Acb

The recent discovery (noted above) that CB1 receptors are found on DA terminals in the Acb and the olfactory tubercle (increasingly recognized as a ventral extension of the Acb vis-a-vis reward functions—see, e.g., Ikemoto, 2003; Ikemoto and Wise, 2004) opens up the distinct possibility that hypothetical models of cannabinoid action on the VTA–MFB–Acb reward axis should re-focus their sights on the Acb (Wenger et al., 2003). Such a refocusing of attention would have at least three benefits. First, such models of direct cannabinoid action on Acb DA-dependent reward substrates would have the appeal of simplicity and parsimony. Second, such models might offer a way around the pernicious difficulties raised for other models by the facts (cited above) that while cannabinoid-induced enhancement of VTA–MFB–Acb DA neuronal firing is *not* attenuated by opiate antagonism (e.g., French, 1997), cannabinoid-induced enhancement of Acb DA is markedly attenuated by opiate antagonism (Chen et al., 1990b; Tanda et al., 1997). Third, such models may be better suited to incorporate additional data relating to cannabinoid actions within the Acb, both directly and inferentially. We shall deal briefly with each of these considerations.

With respect to simplicity and parsimony, it is obvious that models of cannabinoid action on the VTA–MFB–Acb core reward axis that focus on mechanisms closely linked to axon terminal DA release in the Acb would perhaps be the most parsimonious models of all, and attractive on those grounds per se.

With respect to endogenous opioid involvement, models of cannabinoid action on the VTA–MFB–Acb core reward axis that focus on mechanisms closely linked to axon terminal DA release in the Acb would be able to more easily accommodate the observation that opioid antagonism attenuates cannabinoid-enhanced brain-stimulation reward, cannabinoid-enhanced Acb extracellular DA overflow, and cannabinoid self-administration, as such models would eliminate the need to implicate VTA mechanisms in such cannabinoid-induced enhancement of brain reward and reward-linked Acb functions. However, it must be clearly admitted that such models would *not* easily accommodate the finding that cannabinoid-induced enhancement of Acb DA is markedly attenuated by intra-VTA opioid antagonist microperfusion (Tanda et al., 1997). It seems that some form of VTA involvement will, after all, be necessary for any fully attractive explanatory model(s).

With respect to successfully accommodating additional data relating to cannabinoid actions within the Acb, both directly and inferentially, models of cannabinoid action on the VTA–MFB–Acb core reward axis that focus on mechanisms closely linked to axon terminal DA release in the Acb may have their greatest appeal. First, such models would fairly easily accommodate the observations that THC microinjections into the Acb dose-dependently enhance Acb DA while THC microinjections into the VTA (which dose-dependently enhance local VTA DA) do not enhance Acb DA (Chen et al., 1993). Such observations suggest that cannabinoid-enhanced Acb DA (and reward-related functions and behaviors deriving from such enhancement) probably result from local CB1-mediated action(s) within the Acb. Second, such models would fairly easily accommodate an additional observation regarding cannabinoid-enhanced extracellular DA made using in vivo voltammetry (Ng Cheong Ton et al., 1988). In those experiments, in vivo voltammetric electrochemical measurement techniques were used to obtain electrochemical "signatures" of the cannabinoid-evoked extracellular DA overflow. It is well-established that the voltammetric "signature" (in terms of oxidation/reduction ratios and other electrochemical parameters) of DA reuptake blockers is distinctly different, and easily recognizable, from that of presynaptic DA releasers (Gardner et al., 1993). Therefore, in vivo voltammetric electrochemistry was used to measure THC-induced extracellular DA overflow in forebrain DA terminal loci, and showed that the THC-induced electrochemical "signature" resembles that of a DA reuptake blocker rather than that of a presynaptic DA releaser (Ng Cheong Ton et al., 1988). Third, such models would fairly easily accommodate data from additional studies on cannabinoid-enhanced extracel-

lular Acb DA. These additional studies focused on the effects of various combinations of THC and the DA antagonist haloperidol on Acb DA using in vivo brain microdialysis (Gardner et al., 1990b). The rationale for the studies is that impulse-induced facilitation of DA release underlies a synergistic effect between DA antagonists and DA reuptake inhibitors (Westerink et al., 1987). Pretreatment with the DA antagonist haloperidol was found to have a synergistic effect on THC's enhancement of Acb DA, and THC pretreatment before haloperidol had a similar synergistic effect on haloperidol's enhancement of Acb DA (Gardner et al., 1990b). Tetrodotoxin perfused locally into the Acb abolished the synergism between THC and haloperidol (Gardner et al., 1990b). This type of neuropharmacological synergism on extracellular DA is a distinctively characteristic "signature" of co-administration of a DA antagonist and a DA reuptake blocker, such as GBR-12909 (Shore et al., 1979; Westerink et al., 1987). The finding of this characteristic synergistic "signature" when THC and haloperidol were co-administered has a straightforward implication—that THC produces (either directly or indirectly) DA reuptake blockade at Acb DA terminals (Gardner et al., 1990b; Gardner and Lowinson, 1991; Gardner, 1992). Fourth, such models would fairly easily accommodate additional data on cannabinoid-enhanced extracellular Acb DA, gathered from in vivo microdialysis measurements of the DA metabolite 3-methoxytyramine (3-MT) (Chen et al., 1994). While only a relatively minor DA metabolite, 3-MT is uniquely useful for distinguishing DA releasing agents from DA reuptake blockers (Wood and Altar, 1988; Heal et al., 1990). DA releasers such as amphetamine and methamphetamine increase 3-MT levels while DA reuptake blockers such as bupropion and nomifensine do not (Heal et al., 1990). In vivo brain microdialysis experiments were therefore undertaken to directly compare THC's effect on Acb 3-MT levels with those of the benchmark compounds amphetamine, cocaine, and nomifensine. The benchmark DA releaser amphetamine significantly increased *both* DA and 3-MT in Acb, while the benchmark DA reuptake blockers cocaine and nomifensine increased *only* DA. THC increased *only* DA, resembling the DA reuptake blockers (Chen et al., 1994). These in vivo findings are congruent with older in vitro studies showing that cannabinoids have DA reuptake blockade actions in brain tissue, as noted above (Banerjee et al., 1975; Poddar and Dewey, 1980; Hershkowitz and Szechtman, 1979).

10. Endocannabinoid mechanisms in the modulation of brain reward functions

From the many studies and findings cited above, which perforce deal with the effects of *exogenous* cannabinoids on brain reward mechanisms and reward-related behaviors, tentative conclusions may additionally be drawn concerning the manner in which *endocannabinoid* mechanisms may contribute to the regulation and modulation of *endogenous* reward mechanisms in the brain. In fact, it is even possible to postulate specific neural models by which such endocannabinoid regulation of normal reward tone may function. The present author and his colleagues have previously proposed such neural models (e.g., Gardner and Lowinson, 1991; Gardner, 1992), but recent findings have rendered those models less probable and other more recently proposed models, especially by Lupica and his colleagues (Lupica et al., 2004), more probable. Those more recently proposed neural models have been alluded to above. They will be more explicitly described in the following two sections.

10.1. A model of endocannabinoid regulation of reward tone via VTA mechanisms

Lupica et al. (2004) have proposed that, within the VTA, CB1 receptors on afferent GABAergic axon terminals (arising both extrinsically from the Acb and intrinsically within the VTA itself) and on afferent glutamatergic axon terminals play a fundamental role in the regulation of normal reward tone. They propose (on the basis of reasonably well-established electrophysiological and histochemical/anatomical data) that, within the VTA, CB1 receptors regulating normal reward tone are found in three specific locations: (1) on the GABAergic axon terminals arising from cell bodies of GABAergic neurons *intrinsic* to the VTA and synapsing on the intrinsic DA VTA cell bodies, (2) on the GABAergic axon terminals arising *extrinsically* in the Acb (from the medium spiny GABA neurons of the Acb) and synapsing on the intrinsic DA VTA cell bodies, and (3) on the glutamatergic axon terminals arising *extrinsically* (i.e., outside the VTA) and synapsing on the intrinsic DA VTA cell bodies. In this model, endocannabinoid transmitter(s) are released from the VTA DA neuronal cell bodies and travel in retrograde fashion to CB1 receptors on the GABAergic and glutamatergic axon terminals synapsing on the VTA DA neuron. Such retrograde endocannabinoid action could, theoretically, upregulate and downregulate the excitatory and inhibitory synaptic inputs that the VTA DA neuron receives, thus contributing to the probability of neuronal firing of VTA–Acb DA neurons and thus to the regulation of reward tone in the VTA–Acb reward-related circuit. It is important to understand that, in this model, DA neuronal tone is under the control of the GABAergic and glutamatergic inputs to the VTA DA neuron, and the endocannabinoid effect is thus a *modulatory* one—serving perhaps to alter the balance of excitatory/inhibitory input to the VTA DA neuron. Lupica et al. (2004) also propose the presence of μ opioid receptors on the cell bodies of the GABAergic neurons *intrinsic* to the VTA, with endogenous opioid axons synapsing on the intrinsic VTA GABA cell bodies at the sites where the μ opioid receptors are present. This admittedly speculative addition to the model is an attempt to account for the robust evidence (reviewed above)

that the opioid antagonists naloxone and naltrexone block the effects of THC in a wide variety of in vivo paradigms. It is speculated that THC may act on the neural inputs to the μ opioid receptor—thus decreasing GABA release onto the VTA DA neuron and, by a disinhibitory mechanism (e.g., Johnson and North, 1992), enhance DA neuronal activity. This model is attractive, but–as noted previously–fails to account for the apparent lack of action on Acb DA extracellular overflow of cannabinoid microinjection into the VTA (Chen et al., 1993). Also, this model fails to stipulate a satisfactorily *specific* mechanism by which *exogenous cannabinoid* administration activates *endogenous opioid* inputs to the *intrinsic* VTA GABAergic neurons.

10.2. A model of endocannabinoid regulation of reward tone via Acb mechanisms

Lupica et al. (2004) have also proposed (in a model not unlike that stipulated immediately above) that, within the Acb, CB1 receptors on GABAergic axon terminals (arising both from recurrent axon collaterals of the Acb medium spiny neurons and from axon terminals of intrinsic Acb GABA interneurons) and on afferent glutamatergic axon terminals (arising from neocortex, hippocampus, and amygdala) play a fundamental role in the regulation of normal reward tone. They propose (once again on the basis of reasonably well-established electrophysiological and histochemical/anatomical data) that, within Acb, CB1 receptors regulating normal reward tone are found in three specific locations: (1) on GABAergic axon terminals arising from cell bodies of GABAergic interneurons *intrinsic* to Acb and synapsing on Acb medium spiny cell bodies, (2) on GABAergic axon terminals arising *collaterally* in Acb (from the Acb medium spiny GABA neurons) and synapsing back on the intrinsic medium spiny GABA neuronal cell bodies of the Acb, and (3) on the glutamatergic axon terminals arising *extrinsically* (i.e., outside Acb; principally from neocortex, hippocampus, and amygdala) and synapsing into Acb. In this model, endocannabinoid transmitter(s) are released from the Acb GABAergic medium spiny cell bodies and travel in retrograde fashion to CB1 receptors on the GABAergic and glutamatergic axon terminals synapsing on the Acb medium spiny neurons. Such retrograde endocannabinoid action could, theoretically, upregulate and downregulate the excitatory and inhibitory synaptic inputs onto the Acb medium spiny neurons, thus contributing to the probability of neuronal firing of Acb medium spiny neurons and thus (via the Acb GABAergic outputs to VTA; or directly via the neural activity of the medium spiny neurons themselves—see above discussion of the possible homology between medium spiny neural inhibition and reward) to the regulation of reward tone. Once again, as in the case of the previous model centered on the VTA, it is important to understand that in this model, reward tone based upon underlying Acb neuronal tone is under the control of the GABAergic and glutamatergic inputs to the Acb medium spiny neuron, and the endocannabinoid effect is thus a *modulatory* one—serving perhaps to alter the balance of excitatory/inhibitory input to the medium spiny neuron. This model has the merit, assuming that THC acts locally in the Acb via activation of CB1 receptors, of complying both with the disinhibitory mechanistic model of Johnson and North (1992) and the local neuronal site-of-action model of cannabinoid activity that derives from the work of Gardner and colleagues (Chen et al., 1993).

11. Addiction, habit-formation, synaptic plasticity, and endocannabinoid function

One of the major conceptual advances in recent years in the field of addiction research has been a re-centering of attention on the fact that addiction is, at a fundamental level, a disorder of behavioral habit and habit-formation. In these terms, addiction is believed to be a disorder of *DA-dependent* habit-formation (Di Chiara, 1999; Everitt et al., 1999, 2001; Robbins and Everitt, 2002; Wise, 2004). The DA-dependency appears crucial, as DA seems to be essential for the "stamping in" of the response-reward and stimulus-reward associations that underlie the pathognomonic behavioral symptoms of addiction—the aberrantly strong motivational and reinforcing control over behavior of drug-associated stimuli *at the expense of other sources of reinforcement* (Di Chiara, 1999; Everitt et al., 2001; Robbins and Everitt, 2002; Wise, 2004; Wise and Gardner, 2004). Viewed in this way, addiction is a disorder both of reinforcement and of habit-formation, intricately intertwined and perhaps mutually interdependent. This re-centering of attention on the habit-formation and associationistic "stamping in" processes in addiction has led to dramatically increased interest in the types of synaptic modulation or synaptic plasticity that may underlie such aberrant habit-formation. In line with such thinking, it has recently been demonstrated (e.g., Thomas et al., 2001; Robbe et al., 2002; Saal et al., 2003) that addictive drugs alter synaptic plasticity within *both* the core VTA–MFB–Acb reward circuitry *and* in the overlying dorsal neostriatal circuits that have recently been implicated as a crucial site for addiction's *habit-formation* component (see, e.g., Di Chiara, 1999; Everitt et al., 2001; Robbins and Everitt, 2002).

Here again, endocannabinoid function(s) appear to be implicated. Strong evidence that synaptic transmission can be endocannabinoid-dependent, albeit in the hippocampus, was originally presented by Wilson and Nicoll (2001). Following shortly upon that discovery came evidence (Gerdeman et al., 2002) of a link between endocannabinoid function and long-term depression (LTD—a type of synaptic plasticity) in the dorsal striatum (for overview of LTD and long-term potentiation [LTP], see Stanton, 1996; Malenka, 2003; for overview of the "Hebbian" synaptic mechanisms that LTD and LTP may underlie, see Stanton, 1996; Paulsen

and Sejnowski, 2000; Munakata and Pfaffly, 2004; for overview of the possible relationship of such synaptic plasticities to addiction, see Wolf, 2002; Gerdeman et al., 2003; for evidence that such synaptic plasticities may constitute at least a portion of the cellular substrate of reward learning, see Reynolds et al., 2001). Specifically, what Gerdeman et al. (2002) reported was that endocannabinoid function through CB1 receptors was necessary for LTD to be seen in glutamatergic inputs to the GABAergic medium spiny neurons of the dorsal striatum. Subsequently, it was similarly reported that endocannabinoid function through CB1 receptors was necessary for LTD to be seen in glutamatergic inputs to the GABAergic medium spiny neurons of the Acb (Gerdeman et al., 2002, 2003). Furthermore, it was found that endocannabinoid release was associated with the activation of metabotropic glutamate type 5 (mGluR5) receptors, coupled with an increase in markers of synaptic activity in the GABAergic medium spiny neurons (Robbe et al., 2002). In conjunction, these findings seem to show that retrograde endocannabinoid signaling and CB1 receptor activation is necessary for LTD-type synaptic plasticity in both the Acb (core reward pathway) and dorsal neostriatum (containing circuitry proposed to subsume the habit-forming aspects of addiction, and perhaps even to mediate the transition in addiction from reward-driven drug-taking to compulsive non-rewarding habit-driven drug-taking). Bringing many of these considerations of synaptic plasticity in brain loci implicated in addiction back to a grounding with DAergic substrates and mechanisms, it is important to note that DA has been strongly implicated in LTD and LTP for some years. More than a decade ago, Calabresi et al. (1992) demonstrated that DA is importantly involved in neostriatal LTD. In fact, LTD required the presence of DA and the co-activation of D1 and D2 DA receptors. These findings have subsequently been well confirmed (Choi and Lovinger, 1997; Dos Santos Villar and Walsh, 1999; Tang et al., 2001). Provocatively, enhancement of *brain reward* (measured electrophysiologically, in terms of BSR thresholds) may similarly require the co-activation of D1 and D2 DA receptors (Nakajima et al., 1993). Also, LTP requires the activation of DA D1 receptors (Kerr and Wickens, 2001). Although ill-understood at present, the DA role in LTD and LTP may also importantly involve specific *patterns* of DA activity. Thus, *phasic* DA activation may bias neostriatal (and possibly Acb) synapses towards LTP, while *tonic* DA activation may bias the same synapses towards LTD (Reynolds and Wickens, 2002).

The DAergic and endocannabinoid substrates cited above in this section may well be linked. Recent experiments have shown that DA D2 receptor activation stimulates release of the endocannabinoid anandamide (Giuffrida et al., 1999). This release may be depolarization- and calcium-dependent

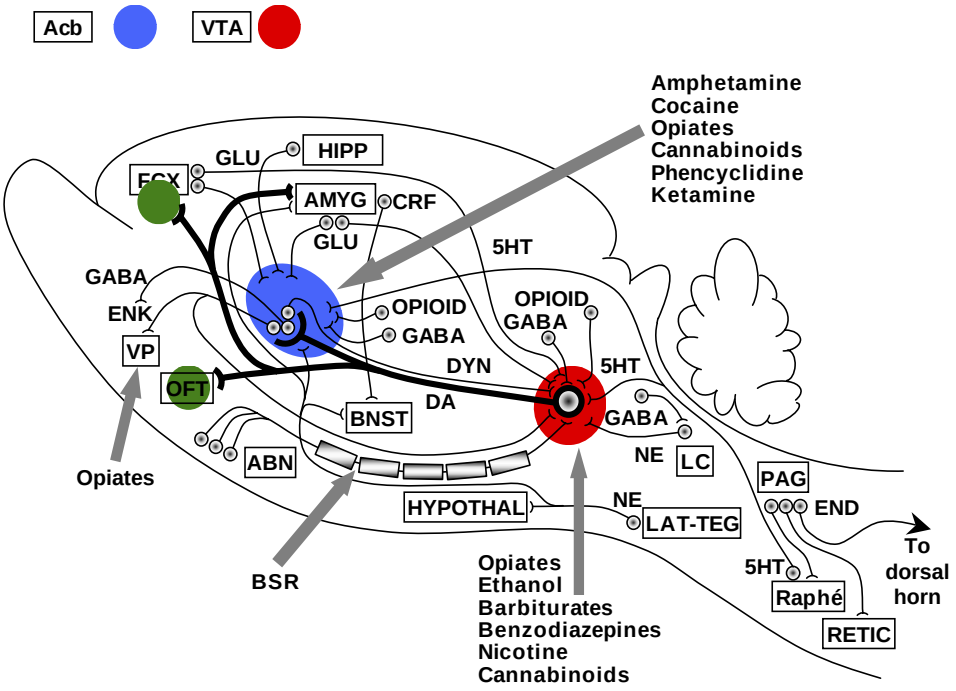

Fig. 1. Diagram of the brain reward circuitry of the mammalian (laboratory rat) brain, indicating sites of action (on the basis of the best presently available evidence) of various drugs, including cannabinoids, that enhance brain reward and reward-related behaviors. ABN, anterior bed nuclei of the medial forebrain bundle; Acb, nucleus accumbens, AMYG, amygdala; BNST, bed nucleus of the stria terminalis; BSR, brain-stimulation reward; CRF, corticotropin releasing factor; DA, dopamine; DYN, dynorphin; END, endorphin; ENK, enkephalin; FCX, frontal cortex; GABA, gamma-aminobutyric acid; GLU, glutamate; HIPP, hippocampus; 5HT, 5-hydroxytryptamine (serotonin); HYPOTHAL, hypothalamus; LAT-TEG, lateral tegmental noradrenergic cell groups; LC, locus coeruleus; NE, norepinephrine (noradrenaline); OFT, olfactory tubercle; OPIOID, endogenous opioid; PAG, periaqueductal grey matter; Raphé, Raphé nuclei of the brain stem; RETIC, reticular formation of the brain stem; VP, ventral pallidum; VTA, ventral tegmental area.

(Di Marzo et al., 1998). At the same time, similar experiments have shown evidence for calcium-*independent* G-protein-mediated enhancement of endocannabinoid release (Ohno-Shosaku et al., 2002). Gerdeman and colleagues have made the provocative suggestion that endocannabinoid synthesis may act as a coincidence detector, detecting coordinated synaptic activity of DA and glutamate on GABAergic medium spiny neurons, resulting in LTD induction (Gerdeman et al., 2003). Bringing such considerations back to drug-taking choice behavior, Montague et al. (1996) have proposed that fluctuations in DA release—mimicking known fluctuations in VTA DA, and relating to predictions about future receipt of reward—may alter synaptic plasticity functions to produce alterations in choice behavior.

Although a comprehensive attempt at integrating exogenous cannabinoid actions on reward mechanisms, endocannabinoid functions, DAergic functions, GABAergic functions, glutamatergic functions, the VTA–MFB–Acb reward axis, the dorsal striatal habit-formation circuitry, drug-seeking and drug-taking in animals, and the clinical phenomena of human drug addiction is far beyond the scope of this brief review, and likely beyond both present-day data and conceptualizations, it seems likely to this author that any satisfactory understanding of the substrates of addiction will require such an integration. Even on the basis of our present-day limited understandings, it appears that such an integration will perforce involve endocannabinoid substrates and mechanisms.

12. Summary

On the basis of extensive behavioral, biochemical, and electrophysiological evidence, cannabinoids appear to enhance brain reward processes and reward-related behaviors in similar fashion to other addictive drugs. Like other drugs with addictive potential, cannabinoids enhance electrical brain-stimulation reward in the core DAergic VTA–MFB–Acb reward system of the brain; enhance neural firing and DA tone within it; produce CPP, a behavioral model of incentive motivation; are self-administered; and trigger relapse to drug-seeking behavior in the reinstatement model—all hallmarks of addictive drug action. Also on the basis of electrophysiological and biochemical evidence, cannabinoid withdrawal appears to activate the same brain withdrawal processes as activated by withdrawal from other addictive drugs. Cannabinoids were long considered different from other addictive drugs, in terms both of addictive potential and underlying neurobiological substrates activated. That stance is no longer supportable, especially in view of recent strong evidence for cannabinoid self-administration in laboratory animals. The exact site(s) and substrate(s) of cannabinoid action in the core VTA–MFB–Acb reward axis and on reward-related behaviors are as yet unclear. While cannabinoids activate the reward pathways in a manner consistent with other addictive drugs, the neural mechanisms by which this occurs may differ. Compelling arguments can be made that cannabinoids enhance brain reward substrates by modulating DA-dependent substrates at the level of the VTA, DA-independent substrates at the level of the Acb, and DA-dependent substrates at the level of the Acb. The recent discovery of CB1 receptors on DA neurons in VTA and Acb make the last of these possibilities more plausible than had been previously thought. Cannabinoid action on brain reward substrates may well involve GABAergic and glutamatergic mechanisms. Endocannabinoids appear importantly implicated in LTD and LTP, two important forms of synaptic plasticity that may underlie the transition from reward-driven behavior to the compulsive habit-driven behavior that characterizes addiction. Any comprehensive and satisfactory attempt to integrate exogenous cannabinoid actions on reward mechanisms, endocannabinoid functions, DAergic functions, GABAergic functions, glutamatergic functions, the VTA–MFB–Acb reward axis, the dorsal striatal habit-formation circuitry, drug-seeking and drug-taking in animals, and the clinical phenomena of human drug addiction must await additional data and advances in conceptualizations. Even on the basis of our current limited understandings, it appears to the present author that such an integration will show endocannabinoid substrates and mechanisms to be some of the most crucial in the entire nervous system.

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References

Aceto MD, Scates SM, Lowe JA, Martin BR. Dependence on delta 9-tetrahydrocannabinol: studies on precipitated and abrupt withdrawal. J Pharmacol Exp Ther 1996;278:1290–5.

Aceto MD, Scates SM, Lowe JA, Martin BR. Spontaneous and precipitated withdrawal from a synthetic cannabinoid, WIN 55,212-2. Eur J Pharmacol 2001;416:75–81.

Alger BE. Retrograde signaling in the regulation of synaptic transmission: focus on endocannabinoids. Prog Neurobiol 2002;68:247–86.

Amit Z, Smith BR, Sutherland EA. Oral self-administration of alcohol: a valid approach to the study of drug self-administration and human

alcoholism. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 161–71.
Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from National Comorbidity Study. Exp Clin Psychopharmacol 1994;2:244–68.
Ashby Jr CR, Rohatgi R, Ngosuwan J, Borda T, Gerasimov MR, Morgan AE, et al. Implication of the $GABA_B$ receptor in gamma vinyl-GABA's inhibition of cocaine-induced increases in nucleus accumbens dopamine. Synapse 1999;31:151–3.
Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J Pharmacol Exp Ther 1975;194:74–81.
Bardo MT. Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. Crit Rev Neurobiol 1998;12:37–67.
Beitner-Johnson D, Guitart X, Nestler EJ. Dopaminergic brain reward regions of Lewis and Fischer rats display different levels of tyrosine hydroxylase and other morphine- and cocaine-regulated phosphoproteins. Brain Res 1991;561:147–50.
Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning or incentive salience? Brain Res Rev 1998;28:309–69.
Bidaut-Russell M, Devane WA, Howlett AC. Cannabinoid receptors and activation of cyclic AMP accumulation in the brain. J Neurochem 1990;55:21–6.
Bindra D. Neuropsychological interpretation of the effects of drive and incentive-motivation on general activity and instrumental behavior. Psychol Rev 1968;75:1–22.
Bloom AS. The effect of Δ^9-tetrahydrocannabinol on the synthesis of dopamine and norepinephrine in mouse brain synaptosomes. J Pharmacol Exp Ther 1982;221:97–103.
Bloom AS, Dewey WL. A comparison of some pharmacological actions of morphine and Δ^9-tetrahydrocannabinol in the mouse. Psychopharmacology 1978;57:243–8.
Bloom AS, Dewey WL, Harris LS, Brosius KK. 9-Nor-9beta-hydroxyhexahydrocannabinol, a cannabinoid with potent antinociceptive activity: comparisons with morphine. J Pharmacol Exp Ther 1977; 200:263–70.
Blum K, Cull JG, Braverman ER, Comings DE. Reward deficiency syndrome. Am Sci 1996;84:132–45.
Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996;89:396–400.
Bozarth MA, Wise RA. Anatomically distinct opiate receptor fields mediate reward and physical dependence. Science 1984;244:516–7.
Brady JV, Lucas SE. Testing drugs for physical dependence potential and abuse liability. NIDA Res Monogr vol. 52. Washington, DC: U.S. Government Printing Office; 1984.
Brady JV, Griffiths RR, Hienz RD, Ator NA, Lukas SE, Lamb RJ. Assessing drugs for abuse liability and dependence potential in laboratory primates. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 45–85.
Braida D, Pozzi M, Cavallini R, Sala M. Conditioned place preference induced by the cannabinoid agonist CP 55,940: interaction with the opioid system. Neuroscience 2001a;104:923–6.
Braida D, Pozzi M, Parolaro D, Sala M. Intracerebral self-administration of the cannabinoid receptor agonist CP 55,940 in the rat: interaction with the opioid system. Eur J Pharmacol 2001b;413:227–34.
Breivogel CS, Griffin G, Di Marzo V, Martin BR. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. Mol Pharmacol 2001;60:155–63.
Cadogan AK, Alexander SP, Boyd EA, Kendall DA. Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. J Neurochem 1997;69:1131–7.
Cador M, Robbins TW, Everitt BJ. Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. Neuroscience 1989;30:77–86.
Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. J Neurosci 1992;12:4224–33.
Cannon DS, Carrell LE. Rat strain differences in ethanol self-administration and taste aversion. Pharmacol Biochem Behav 1987;28:57–63.
Carlezon Jr WA, Wise RA. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. J Neurosci 1996a;16:3112–22.
Carlezon Jr WA, Wise RA. Microinjections of phencyclidine (PCP) and related drugs into nucleus accumbens shell potentiate medial forebrain bundle brain stimulation reward. Psychopharmacology 1996b;128:413–20.
Carney JM, Uwaydah IM, Balster RL. Evaluation of a suspension system for intravenous self-administration of water insoluble substances in the rhesus monkey. Pharmacol Biochem Behav 1977;7:357–64.
Castañeda E, Moss DE, Oddie SD, Whishaw IQ. THC does not affect striatal dopamine release: microdialysis in freely moving rats. Pharmacol Biochem Behav 1991;40:587–91.
Chaperon F, Soubrié P, Puech AJ, Thiébot M-H. Involvement of central cannabinoid (CB_1) receptors in the establishment of place conditioning in rats. Psychopharmacology 1998;135:324–32.
Cheer JF, Kendall DA, Marsden CA. Cannabinoid receptors and reward in the rat: a conditioned place preference study. Psychopharmacology 2000a;151:25–30.
Cheer JF, Marsden CA, Kendall DA, Mason R. Lack of response suppression follows repeated ventral tegmental cannabinoid administration: an in vitro electrophysiological study. Neuroscience 2000b; 99:661–7.
Chen J, Paredes W, Li J, Smith D, Gardner EL. In vivo brain microdialysis studies of Δ^9-tetrahydrocannabinol on presynaptic dopamine efflux in nucleus accumbens of the Lewis rat. Soc Neurosci Abstr 1989;15:1096.
Chen J, Paredes W, Lowinson JH, Gardner EL. Δ^9-Tetrahydrocannabinol enhances presynaptic dopamine efflux in medial prefrontal cortex. Eur J Pharmacol 1990a;190:259–62.
Chen J, Paredes W, Li J, Smith D, Lowinson J, Gardner EL. Δ^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 1990b;102:156–62.
Chen J, Paredes W, Lowinson JH, Gardner EL. Strain-specific facilitation of dopamine efflux by Δ^9-tetrahydrocannabinol in the nucleus accumbens of rat: an in vivo microdialysis study. Neurosci Lett 1991;129:136–40.
Chen J, Marmur R, Pulles A, Paredes W, Gardner EL. Ventral tegmental microinjection of Δ^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;621:65–70.
Chen J, Paredes W, Gardner EL. Δ^9-Tetrahydrocannabinol's enhancement of nucleus accumbens dopamine resembles that of reuptake blockers rather than releasers—evidence from in vivo microdialysis experiments with 3-methoxytyramine. NIDA Res Monogr 1994;141:312.
Chieng B, Williams JT. Increased opioid inhibition of GABA release in nucleus accumbens during morphine withdrawal. J Neurosci 1998; 18:7033–9.
Childers SR, Fleming L, Konkoy C, Marckel D, Pacheco M, Sexton T, et al. Opioid and cannabinoid receptor inhibition of adenylyl cyclase in brain. Ann N Y Acad Sci 1992;654:33–51.
Choi S, Lovinger DM. Decreased probability of neurotransmitter release underlies striatal long-term depression and postnatal development of corticostriatal synapses. Proc Natl Acad Sci U S A 1997;94:2665–70.
Cook SA, Lowe JA, Martin BR. CB1 receptor antagonist precipitates withdrawal in mice exposed to Δ^9-tetrahydrocannabinol. J Pharmacol Exp Ther 1998;285:1150–6.

Corcoran ME, Amit Z. Reluctance of rats to drink hashish suspensions: free-choice and forced consumption, and the effects of hypothalamic stimulation. Psychopharmacologia 1974;35:129–47.

Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. Drug Alcohol Depend 1998;50:27–37.

Deneau GA, Kaymakçalan S. Physiological and psychological dependence to synthetic Δ^9-tetrahydrocannabinol (THC) in rhesus monkeys. Pharmacologist 1971;13:246.

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.

Dewey SL, Morgan AE, Ashby Jr CR, Horan B, Kushner SA, Logan J, et al. A novel strategy for the treatment of cocaine addiction. Synapse 1998;30:119–29.

Dewey SL, Brodie JD, Gerasimov M, Horan B, Gardner EL, Ashby Jr CR. A pharmacologic strategy for the treatment of nicotine addiction. Synapse 1999;31:76–86.

de Wit H, Stewart J. Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology 1981;75:134–43.

de Wit H, Stewart J. Drug reinstatement of heroin-reinforced responding in the rat. Psychopharmacology 1983;79:29–31.

Diana M, Melis M, Gessa GL. Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur J Neurosci 1998a;10:2825–30.

Diana M, Melis M, Muntoni AL, Gessa GL. Mesolimbic dopaminergic decline after cannabinoid withdrawal. Proc Natl Acad Sci U S A 1998b;95:10269–73.

Di Chiara G. The role of dopamine in drug abuse viewed from the perspective of its role in motivation. Drug Alcohol Depend 1995; 38:95–137.

Di Chiara G. Drug addiction as dopamine-dependent associative learning disorder. Eur J Pharmacol 1999;375:13–30.

Di Chiara G, Imperato A. Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with transcerebral dialysis in freely moving rats. Ann N Y Acad Sci 1986;473:367–81.

Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends Neurosci 1998;21:521–8.

Dos Santos Villar F, Walsh JP. Modulation of long-term synaptic plasticity at excitatory striatal synapses. Neuroscience 1999;90:1031–41.

Erb S, Shaham Y, Stewart J. Stress reinstates cocaine-seeking behavior after prolonged extinction and drug-free periods. Psychopharmacology 1996;128:408–12.

Everitt BJ, Cador M, Robbins TW. Interactions between the amygdala and ventral striatum in stimulus-reward associations: studies using a second-order schedule of sexual reinforcement. Neuroscience 1989; 30:63–75.

Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW. Associative processes in addiction and reward: the role of amygdala–ventral striatal subsystems. Ann N Y Acad Sci 1999; 877:412–38.

Everitt BJ, Dickinson A, Robbins TW. The neuropsychological basis of addictive behaviour. Brain Res Rev 2001;36:129–38.

Felder CC, Glass M. Cannabinoid receptors and their endogenous agonists. Annu Rev Pharmacol Toxicol 1998;38:179–200.

Frank RA, Martz S, Pommering T. The effect of chronic cocaine on self-stimulation train-duration thresholds. Pharmacol Biochem Behav 1988;29:755–8.

Fratta W, Martellotta MC, Cossu G, Fattore L. WIN 55,212-2 induces intravenous self-administration in drug-naive mice. Soc Neurosci Abstr 1997;23:1869.

French ED. Δ^9-Tetrahydrocannabinol excites rat VTA dopamine neurons through activation of cannabinoid CB1 but not opioid receptors. Neurosci Lett 1997;226:159–62.

French ED, Dillon K, Wu X. Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. Neuroreport 1997;8:649–52.

Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83:1017–66.

Fudala PJ, Iwamoto ET. Conditioned aversion after delay place conditioning with amphetamine. Pharmacol Biochem Behav 1990;35:89–92.

Fudala PJ, Teoh KW, Iwamoto ET. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol Biochem Behav 1985;22:237–41.

Gaffan D. Amygdala and the memory of reward. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion. New York: Wiley; 1992. p. 471–83.

Gallistel CR, Shizgal P, Yeomans JS. A portrait of the substrate for self-stimulation. Psychol Rev 1981;88:228–73.

Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964;86:1646.

Gardner EL. Cannabinoid interaction with brain reward systems—the neurobiological basis of cannabinoid abuse. In: Murphy LL, Bartke A, editors. Marijuana/cannabinoids: neurobiology and neurophysiology. New York: CRC; 1992. p. 275–335.

Gardner EL. Brain reward mechanisms. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG, editors. Substance abuse: a comprehensive textbook, 3rd edn. Baltimore: Williams & Wilkins; 1997. p. 51–85.

Gardner EL. The neurobiology and genetics of addiction: implications of the "reward deficiency syndrome" for therapeutic strategies in chemical dependency. In: Elster J, editor. Addiction: entries and exits. New York: Russell Sage; 1999. p. 57–119.

Gardner EL. What we have learned about addiction from animal models of drug self-administration. Am J Addict 2000;9:285–313.

Gardner EL, Lowinson JH. Marijuana's interaction with brain reward systems: update 1991. Pharmacol Biochem Behav 1991;40:571–80.

Gardner EL, Lowinson JH. Drug craving and positive/negative hedonic brain substrates activated by addicting drugs. Semin Neurosci 1993;5:359–68.

Gardner EL, Vorel SR. Cannabinoid transmission and reward-related events. Neurobiol Dis 1998;5:502–33.

Gardner EL, Paredes W, Smith D, Donner A, Milling C, Cohen D, et al. Facilitation of brain stimulation reward by Δ^9-tetrahydrocannabinol. Psychopharmacology 1988a;96:142–4.

Gardner EL, Paredes W, Smith D, Seeger T, Donner A, Milling C, et al. Strain-specific sensitization of brain stimulation reward by Δ^9-tetrahydrocannabinol in laboratory rats. Psychopharmacology 1988b;96:365 [suppl.].

Gardner EL, Chen J, Paredes W, Li J, Smith D. Strain-specific facilitation of brain stimulation reward by Δ^9-tetrahydrocannabinol in laboratory rats is mirrored by strain-specific facilitation of presynaptic dopamine efflux in nucleus accumbens. Soc Neurosci Abstr 1989a;15:638.

Gardner EL, Paredes W, Smith D, Zukin RS. Facilitation of brain stimulation reward by Δ^9-tetrahydrocannabinol is mediated by an endogenous opioid mechanism. Adv Biosci 1989b;75:671–4.

Gardner EL, Chen J, Paredes W, Smith D, Li J, Lowinson J. Enhancement of presynaptic dopamine efflux in brain by Δ^9-tetrahydrocannabinol is mediated by an endogenous opioid mechanism. In: van Ree AH, Mulder AH, Wiegant VM, van Wimersma Greidanus TB, editors. New leads in opioid research. Amsterdam: Elsevier; 1990a. p. 243–5.

Gardner EL, Paredes W, Chen J. Further evidence for Δ^9-tetrahydrocannabinol as a dopamine reuptake blocker: brain microdialysis studies. Soc Neurosci Abstr 1990b;16:1100.

Gardner EL, Chen J, Paredes W. Overview of chemical sampling techniques. J Neurosci Methods 1993;48:173–97.

George FR. Genetic and environmental factors in ethanol self-administration. Pharmacol Biochem Behav 1987;27:379–84.

George FR, Goldberg SR. Genetic approaches to the analysis of addiction processes. Trends Pharmacol Sci 1989;10:78–83.

George FR, Meisch RA. Oral narcotic intake as a reinforcer: genotype × environment interaction. Behav Genet 1984;14:603.

Gerdeman GL, Ronesi J, Lovinger DM. Post-synaptic 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.

Gessa GL, Diana M. Different mechanisms for dopaminergic excitation induced by opiates and cannabinoids in the rat midbrain. Prog Neuropsychopharmacol Biol Psychiatry 2000;24:993–1006.

Gessa GL, Melis M, Muntoni AL, Diana M. Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB_1 receptors. Eur J Pharmacol 1998;341:39–44.

Gifford AN, Gardner EL, Ashby Jr CR. The effect of intravenous administration of delta-Δ^9-tetrahydrocannabinol on the activity of A10 dopamine neurons recorded in vivo in anesthetized rats. Neuropsychobiology 1997;36:96–9.

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

Goldstein A. Addiction: from biology to drug policy. 2nd ed. New York: Oxford University Press; 2001.

Goldstein A, Kalant H. Drug policy: striking the right balance. Science 1990;249:1513–21.

Gonon FG. Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry. Neuroscience 1988;24:19–28.

Grenhoff J, Aston-Jones G, Svensson TH. Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol Scand 1986;128:351–8.

Griffiths RR, Bigelow CE, Liebson I. Experimental drug self-administration: generality across species and type of drug. NIDA Res Monogr 1978;20:24–43.

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

Guitart X, Beitner-Johnson D, Marby DW, Kosten TA, Nestler EJ. Fischer and Lewis rat strains differ in basal levels of neurofilament proteins and in their regulation by chronic morphine in the mesolimbic dopamine system. Synapse 1992;12:242–53.

Guitart X, Kogan JH, Berhow M, Terwilliger RZ, Aghajanian GK, Nestler EJ. Lewis and Fischer rat strains display differences in biochemical, electrophysiological and behavioral parameters: studies in the nucleus accumbens and locus coeruleus of drug naive and morphine-treated animals. Brain Res 1993;611:7–17.

Gysling K, Wang RY. Morphine-induced activation of A10 dopamine neurons in the rat. Brain Res 1983;277:119–27.

Hajos N, Freund TF. Pharmacological separation of cannabinoid sensitive receptors on hippocampal excitatory and inhibitory fibers. Neuropharmacology 2002;43:503–10.

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

Hall W, Solowij N, Lemon J, 1994. The health and psychological consequences of cannabis use. National Drug Strategy Monograph Series vol. 25. Canberra: Australian Government Publishing Service; 1994.

Harris RT, Waters W, McLendon D. Evaluation of reinforcing capability of Δ^9-tetrahydrocannabinol in monkeys. Psychopharmacologia 1974; 37:23–9.

Harvey J, Lacey MG. A postsynaptic interaction between dopamine D_1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. J Neurosci 1997;17:5271–80.

Hayes RJ, Vorel SR, Spector J, Liu X, Gardner EL. Electrical and chemical stimulation of the basolateral complex of the amygdala reinstates cocaine-seeking behavior. Psychopharmacology 2003;168:75–83.

Heal DJ, Frankland ATJ, Buckett WR. A new and highly sensitive method for measuring 3-methoxytyramine using HPLC with electrochemical detection: studies with drugs which alter dopamine metabolism in the brain. Neuropharmacology 1990;29:1141–50.

Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity of the projection patterns of accumbal core and shell in the rat. Neuroscience 1991;41:89–125.

Henry DJ, Chavkin C. Activation of inwardly rectifying potassium channels (GIRK1) by co-expressed rat brain cannabinoid receptors in Xenopus oocytes. Neurosci Lett 1995;186:91–4.

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 1990;87:1932–6.

Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci 1991; 11:563–83.

Hershkowitz M, Szechtman H. Pretreatment with Δ^1-tetrahydrocannabinol and psychoactive drugs: effects on uptake of biogenic amines and on behavior. Eur J Pharmacol 1979;59:267–76.

Hershkowitz M, Goldman R, Raz A. Effect of cannabinoids on neurotransmitter uptake, ATPase activity and morphology of mouse brain synaptosomes. Biochem Pharmacol 1977;26:1327–31.

Hiroi N, White NM. The lateral nucleus of the amygdala mediates expression of the amphetamine conditioned place preference. J Neurosci 1991;11:2107–16.

Hoffman AF, Lupica CR. Mechanisms of cannabinoid inhibition of $GABA_A$ synaptic transmission in the hippocampus. J Neurosci 2000; 20:2470–9.

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.

Hohmann AG, Herkenham M. Localization of cannabinoid CB1 receptor mRNA in neuronal subpopulations of rat striatum: a double-label in situ hybridization study. Synapse 2000;37:71–80.

Hutcheson DM, Tzavara ET, Smadja C, Valjent E, Roques BP, Hanoune J, et al. Behavioural and biochemical evidence for signs of abstinence in mice chronically treated with Δ^9-tetrahydrocannabinol. Br J Pharmacol 1998;125:1567–77.

Ikemoto S. Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. J Neurosci 2003;23:9305–11.

Ikemoto S, Wise RA. Mapping of chemical trigger zones for reward. Neuropharmacology 2004;47:190–201.

Jentsch JD, Wise A, Katz Z, Roth RH. Alpha-noradrenergic receptor modulation of the phencyclidine- and Δ^9-tetrahydrocannabinol-induced increases in dopamine utilization in rat prefrontal cortex. Synapse 1998;28:21–6.

Johnson KM, Dewey WL, Harris LS. Some structural requirements for inhibition of high-affinity synaptosomal serotonin uptake by cannabinoids. Mol Pharmacol 1976;12:345–52.

Johnson PI, Goodman JB, Condon R, Stellar JR. Reward shifts and motor responses following microinjections of opiate-specific agonists into either the core or shell of the nucleus accumbens. Psychopharmacology 1995;120:195–202.

Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci 1992;12:483–8.

Jorenby DE, Steinpreis RE, Sherman JE, Baker TB. Aversion instead of preference learning indicated by nicotine place conditioning in rats. Psychopharmacology 1990;101:533–8.

Justinova Z, Tanda G, Redhi GH, Goldberg SR. Self-administration of Δ^9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. Psychopharmacology 2003;169:135–40.

Justinova Z, Tanda G, Munzar P, Goldberg SR. The opioid antagonist naltrexone reduces the reinforcing effects of Δ^9-tetrahydrocannabinol (THC) in squirrel monkeys. Psychopharmacology 2004;173: 186–94.

Katner SN, Magalong JG, Weiss F. Reinstatement of alcohol-seeking behavior by drug-associated discriminative stimuli after prolonged extinction in the rat. Neuropsychopharmacology 1999;20:471–9.

Kaymakçalan S. Physiology and psychological dependence on THC in rhesus monkeys. In: Paton WDM, Crown J, editors. Cannabis and its derivatives. London: Oxford University; 1972. p. 142–9.

Kaymakçalan S. Tolerance to and dependence on cannabis. Bull Narc 1973;25:39–47.

Kerr JN, Wickens JR. Dopamine D-1/D-5 receptor activation is required for long-term potentiation in the rat neostriatum in vitro. J Neurophysiol 2001;85:117–24.

Khodzhagel'diev T. Formirovanie vlecheniia k nikotinu u myshei linii C57Bl/6 i CBA [Development of nicotine preference in C57Bl/6 and CBA mice]. Biull Eksp Biol Med 1986;101:48–50.

Kitai ST, Shepard PD, Callaway JC, Scroogs R. Afferent modulation of dopamine neuron firing patterns. Curr Opin Neurobiol 1999;9:690–7.

Kleber HD. Introduction—cocaine abuse: historical, epidemiological, and psychological perspectives. J Clin Psychiatry 1988;49(2):3–6 [suppl.].

Koob GF. Drug addiction: the yin and yang of hedonic homeostasis. Neuron 1996;16:893–6.

Koob GF. The role of the striatopallidal and extended amygdala systems in drug addiction. Ann N Y Acad Sci 1999;877:445–60.

Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science 1997;278:52–8.

Koob GF, Markou A, Weiss F, Schulteis G. Opponent process and drug dependence: neurobiological mechanisms. Semin Neurosci 1993; 5:351–8.

Koós T, Tepper JM. Inhibitory control of neostriatal projection neurons by GABAergic interneurons. Nat Neurosci 1999;2:467–72.

Kornetsky C, Bain G. Brain-stimulation reward: a model for the study of the rewarding effects of abused drugs. NIDA Res Monogr 1992; 124:73–93.

Kornetsky C, Duvauchelle C. Dopamine, a common substrate for the rewarding effects of brain stimulation reward, cocaine, and morphine. NIDA Res Monogr 1994;145:19–39.

Kosten TA, Miserendino MJ, Chi S, Nestler EJ. Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. J Pharmacol Exp Ther 1994;269:137–44.

Kosten TA, Miserendino MJ, Haile CN, DeCaprio JL, Jatlow PI, Nestler EJ. Acquisition and maintenance of intravenous cocaine self-administration in Lewis and Fischer inbred rat strains. Brain Res 1997;778:418–29.

Kozel NJ, Adams EH. Epidemiology of drug abuse: an overview. Science 1986;234:970–4.

Laszlo J, Lucas VS, Hanson DC, Cronin CM, Sallan SE. Levonantradol for chemotherapy-induced emesis: phase I–II oral administration. J Clin Pharmacol 1981;21(8–9):51S–6S [suppl.].

Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB_1 receptor knockout mice. Science 1999;283:401–4.

Leite JR, Carlini EA. Failure to obtain "cannabis directed behavior" and abstinence syndrome in rats chronically treated with *Cannabis sativa* extracts. Psychopharmacologia 1974;36:133–45.

Lepore M, Vorel SR, Lowinson J, Gardner EL. Conditioned place preference induced by Δ^9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. Life Sci 1995;56:2073–80.

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 1996; 58:PL365–72.

Lupica CR, Riegel AC, Hoffman AF. Marijuana and cannabinoid regulation of brain reward circuits. Br J Pharmacol 2004;143:227–34.

MacCoun R, Reuter P. Interpreting Dutch cannabis policy: reasoning by analogy in the legalization debate. Science 1997;278:47–52.

Malenka RC. Synaptic plasticity and AMPA receptor trafficking. Ann N Y Acad Sci 2003;1003:1–11.

Mallet PE, Beninger RJ. Δ^9-Tetrahydrocannabinol, but not the endogenous cannabinoid receptor ligand anandamide, produces conditioned place aversion. Life Sci 1998;62:2431–9.

Malone DT, Taylor DA. Modulation by fluoxetine of striatal dopamine release following Δ^9-tetrahydrocannabinol: a microdialysis study in conscious rats. Br J Pharmacol 1999;128:21–6.

Mansbach RS, Nicholson KL, Martin BR, Balster RL. Failure of Δ^9-tetrahydrocannabinol and CP 55,940 to maintain intravenous self-administration under a fixed-interval schedule in rhesus monkeys. Behav Pharmacol 1994;5:219–25.

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

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.

Martin G, Nie Z, Siggins GR. μ-Opioid receptors modulate NMDA receptor-mediated responses in nucleus accumbens neurons. J Neurosci 1997;17:11–22.

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.

McBride WJ, Murphy JM, Ikemoto S. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav Brain Res 1999;101:129–52.

McFarland K, Ettenberg A. Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli. Psychopharmacology 1997;131:86–92.

McGregor IS, Issakidis CN, Prior G. Aversive effects of the synthetic cannabinoid CP 55,940 in rats. Pharmacol Biochem Behav 1996;53:657–64.

Mchoulam R, Fride E, Di Marzo V. Endocannabinoids. Eur J Pharmacol 1998;359:1–18.

Meil WM, See RE. Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. Behav Pharmacol 1996;7:754–63.

Meisch RA, Carroll ME. Oral drug self-administration: drugs as reinforcers. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 143–60.

Melis M, Muntoni AL, Diana M, Gessa GL. The cannabinoid receptor agonist WIN 55,212-2 potently stimulates dopaminergic neuronal activity in the mesolimbic system. Behav Pharmacol 1996;7(suppl. 1): 68.

Melis M, Pistis M, Perra S, Muntoni AL, Pillolla G, Gessa GL. Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in the rat ventral tegmental area dopamine neurons through activation of CB1 receptors. J Neurosci 2004;24:53–62.

Merlo Pich E, Lorang M, Yeganeh M, Rodríguez de Fonseca F, Raber J, Koob GF, et al. Increase in extracellular corticotropin-releasing factor-like immunoreactivity levels in the amygdala of awake rats during restraint stress and ethanol withdrawal as measured by microdialysis. J Neurosci 1995;15:5439–47.

Montague PR, Dayan P, Sejnowski TJ. A framework for mesencepahlic dopamine systems based on predictive Hebbian learning. J Neurosci 1996;16:1936–47.

Mucha RF, van der Kooy D, O'Shaughnessy M, Bucenieks P. Drug reinforcement studied by use of place conditioning in rat. Brain Res 1982;243:91–105.

Munakata Y, Pfaffly J. Hebbian learning and development. Dev Sci 2004;7:141–8.

Nakajima S, Liu X, Lau CL. Synergistic interaction of D1 and D2 dopamine receptors in the modulation of the reinforcing effect of brain stimulation. Behav Neurosci 1993;107:161–5.

Napier TC, Mitrovic I. Opioid modulation of ventral pallidal inputs. Ann N Y Acad Sci 1999;877:176–201.

Navarro M, Fernández-Ruiz JJ, de Miguel R, Hernández ML, Cebeira M, Ramos JA. An acute dose of Δ^9-tetrahydrocannabinol affects behavioral and neurochemical indices of mesolimbic dopaminergic activity. Behav Brain Res 1993;57:37–46.

Navarro M, Chowen J, Carrera MRA, del Arco I, Villanúa MA, Martin Y, et al. CB_1 cannabinoid receptor antagonist-induced opiate withdrawal in morphine-dependent rats. Neuroreport 1998;9:3397–402.

Nestler EJ. Molecular mechanisms of drug addiction in the mesolimbic dopamine pathway. Semin Neurosci 1993;5:369–76.

Ng Cheong Ton JM, Gardner EL. Effects of delta-9-tetrahydrocannabinol on dopamine release in the brain: intracranial dialysis experiments. Soc Neurosci Abstr 1986;12:135.

Ng Cheong Ton JM, Gerhardt GA, Friedemann M, Etgen AM, Rose GM, Sharpless NS, et al. The effects of Δ^9-tetrahydrocannabinol on potassium-evoked release of dopamine in the rat caudate nucleus: an in vivo electrochemical and in vivo microdialysis study. Brain Res 1988;451:59–68.

Nicola SM, Malenka RC. Modulation of synaptic transmission by dopamine and norepinephrine in ventral but not dorsal striatum. J Neurophysiol 1998;79:1768–76.

Noyes JR, Brunk SF, Avery DH, Canter A. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975;18:84–9.

Ohno-Shosaku T, Shosaku J, Tsubokawa H, Kano M. Cooperative endocannabinoid production by neuronal depolarization and group I metabotropic glutamate receptor activation. Eur J Neurosci 2002; 15:953–61.

Overton PG, Clark D. Burst firing in midbrain dopaminergic neurons. Brain Res Rev 1997;25:312–34.

Parker LA, Gillies T. THC-induced place and taste aversions in Lewis and Sprague–Dawley rats. Behav Neurosci 1995;109:71–8.

Parsons LH, Smith AD, Justice Jr JB. Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse 1991;9:60–5.

Paulsen O, Sejnowski TJ. Natural patterns of activity and long-term synaptic plasticity. Curr Opin Neurobiol 2000;10:172–9.

Peoples LL, Uzwiak AJ, Gee F, Fabbricatore AT, Muccino KJ, Mohta BD, et al. Phasic accumbal firing may contribute to the regulation of drug taking during intravenous cocaine self-administration. Ann N Y Acad Sci 1999;877:781–7.

Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther 1997;74:129–80.

Pickens R, Thompson T, Muchow DC. Cannabis and phencyclidine self-administered by animals. In: Goldfarb L., Hoffmeister F., editors. Psychic dependence [Bayer-Symposium IV]. Berlin: Springer-Verlag; 1973. p. 78–86.

Plenz D. Inhibition goes incognito: feedback interaction between spiny projection neurons in striatal function. Trends Neurosci 2003;26: 436–43.

Poddar MK, Dewey WL. Effects of cannabinoids on catecholamine uptake and release in hypothalamus and striatal synaptosomes. J Pharmacol Exp Ther 1980;214:63–7.

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 U S A 1995;92:12304–8.

Pothos E, Rada P, Mark GP, Hoebel BG. Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. Brain Res 1991; 566:348–50.

Raft D, Gregg J, Ghia J, Harris L. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlate of the analgesic response. Clin Pharmacol Ther 1977;21: 26–33.

Redgrave P, Prescott TJ, Gurney K. Is the short-latency dopamine response too short to signal reward error? Trends Neurosci 1999; 22:146–51.

Reynolds JNJ, Wickens JR. Dopamine-dependent plasticity of corticostriatal synapses. Neural Netw 2002;15:507–21.

Reynolds JNJ, Hyland BI, Wickens JR. A cellular mechanism of reward-related learning. Nature 2001;413:67–70.

Richardson NR, Roberts DCS. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J Neurosci Methods 1996;66:1–11.

Riegel AC, Williams JT, Lupica CR. Cannabinoid CB1 receptors inhibit $GABA_B$-mediated synaptic currents in midbrain dopamine neurons. Paper presented at meetings of the Society for Neuroscience, New Orleans, Louisiana, November 2003. (Abstract published in 2003 Abstract Viewer/Itinerary Planner CD-ROM, the Thirty-Third Annual Meeting of the Society for Neuroscience, New Orleans, Louisiana, November 812, 2003, Society for Neuroscience, Washington, D.C., Program Abstract Number 462.6).

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.

Robbins TW, Everitt BJ. Limbic–striatal memory systems and drug addiction. Neurobiol Learn Mem 2002;78:625–36.

Roberts DCS, Andrews MM, Vickers GJ. Baclofen attenuates the reinforcing effects of cocaine. Neuropsychopharmacology 1996; 15:417–23.

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

Rodríguez de Fonseca F, Carrera MRA, Navarro M, Koob GF, Weiss F. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. Science 1997;276:2050–4.

Rossetti ZL, Hmaidan Y, Gessa GL. Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur J Pharmacol 1992;221: 227–34.

Rubino T, Tizzoni L, Viganò D, Massi P, Parolaro D. Modulation of rat brain cannabinoid receptors after chronic morphine treatment. Neuroreport 1997;8:3219–23.

Saal D, Dong Y, Bonci A, Malenka RC. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. Neuron 2003; 37:577–82.

Sañudo-Peña MC, Tsou K, Delay ER, Hohman AG, Force M, Walker JM. Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. Neurosci Lett 1997;223:125–8.

Schaefer GJ, Michael RP. Changes in response rates and reinforcement thresholds for intracranial self-stimulation during morphine withdrawal. Pharmacol Biochem Behav 1986;25:1263–9.

Schechter MD, Calcagnetti DJ. Trends in place preference conditioning with a cross-indexed bibliography; 1957–1991. Neurosci Biobehav Rev 1993;17:21–41.

Schulteis G, Markou A, Gold LH, Stinus L, Koob GF. Relative sensitivity of multiple indices of opiate withdrawal: a quantitative dose–response analysis. J Pharmacol Exp Ther 1994;271:1391–8.

Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997;275:1593–9.

Self DW, Nestler EJ. Molecular mechanisms of drug reinforcement and addiction. Annu Rev Neurosci 1995;18:463–95.

Shaham Y, Stewart J. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology 1995;119:334–41.

Shaham Y, Rajabi H, Stewart J. Relapse to heroin-seeking in rats under opioid maintenance: the effects of stress, heroin-priming, and withdrawal. J Neurosci 1996;16:1957–63.

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

Shizgal P. Neural basis of utility estimation. Curr Opin Neurobiol 1997;7:198–208.

Shore PA, McMillen BA, Miller HH, Sanghera MK, Kiserand RS, German DC. The dopamine neuronal storage system and non-amphetamine psychotogenic stimulants: a model for psychosis. In: Usdin E, Kopin IJ, Barchas J, editors. Catecholamines: basic and clinical frontiers. New York: Pergamon Press; 1979. p. 722–35.

Simon D, Burns E. The corner: a year in the life of an inner-city neighborhood. New York: Broadway Books (Random House); 1997.

Stanton PK. LTD, LTP, and the sliding threshold for long-term synaptic plasticity. Hippocampus 1996;6:35–42.
Stewart J. Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. Pharmacol Biochem Behav 1984;20:917–23.
Stewart J, de Wit H. Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 211–27.
Stewart J, Vezina P. A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. Brain Res 1988;457: 287–294.
Sugita S, Johnson SW, North RA. Synaptic inputs to $GABA_A$ and $GABA_B$ receptors originate from discrete afferent neurons. Neurosci Lett 1992;134:207–11.
Suzuki T, George FR, Meisch RA. Differential establishment and maintenance of oral ethanol reinforced behavior in Lewis and Fischer 344 inbred rat strains. J Pharmacol Exp Ther 1989;245:164–70.
Szabo B, Muller T, Koch H. Effects of cannabinoids on dopamine release in the corpus striatum and the nucleus accumbens in vitro. J Neurochem 1999;73:1084–9.
Szabo B, Siemes S, Wallmichrath I. Inhibition of GABAergic neurotransmission in the ventral tegmental area by cannabinoids. Eur J Neurosci 2002;15:2057–61.
Takahashi RN, Singer G. Self-administration of Δ^9-tetrahydrocannabinol by rats. Pharmacol Biochem Behav 1979;11:737–40.
Takahashi RN, Singer G. Effects of body weight levels on cannabis self-administration. Pharmacol Biochem Behav 1980;13:877–81.
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.
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.
Tanda G, Loddo P, Di Chiara G. Dependence of mesolimbic dopamine transmission on Δ^9-tetrahydrocannabinol. Eur J Pharmacol 1999; 376:23–6.
Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient in marijuana in squirrel monkeys. Nat Neurosci 2000;3:1073–4.
Tang K-C, Low MJ, Grandy DK, Lovinger DM. Dopamine-dependent synaptic plasticity in striatum during in vivo development. Proc Natl Acad Sci U S A 2001;98:1255–60.
Taylor DA, Sitaram BR, Elliot-Baker S. Effect of Δ-9-tetrahydrocannabinol on release of dopamine in the corpus striatum of the rat. In: Chesher G, Consroe P, Musty R, editors. Marijuana: an international research report. Canberra: Australian Government Publishing; 1988. p. 405–8.
Thanos PK, Volkow ND, Freimuth P, Umegaki H, Ikari H, Roth G, et al. Overexpression of dopamine D2 receptors reduces alcohol self-administration. J Neurochem 2001;78:1094–103.
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.
Thorat SN, Bhargava HN. Evidence for a bidirectional cross-tolerance between morphine and Δ^9-tetrahydrocannabinol in mice. Eur J Pharmacol 1994;260:5–13.
Tsou K, Patrick SL, Walker JM. Physical withdrawal in rats tolerant to delta 9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. Eur J Pharmacol 1995;280:R13–5.
Twitchell W, Brown S, Mackie K. Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. J Neurophysiol 1997;78:43–50.
Tzavara ET, Valjent E, Firmo C, Mas M, Beslot F, Defer N, et al. Cannabinoid withdrawal is dependent upon PKA activation in the cerebellum. Eur J Neurosci 2000;12:1038–46.
Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol 1998;56:613–72.
Uhl G, Blum K, Noble E, Smith S. Substance abuse vulnerability and D2 receptor genes. Trends Neurosci 1993;16:83–8.
Valjent E, Maldonado R. A behavioural model to reveal place preference to Δ^9-tetrahydrocannabinol in mice. Psychopharmacology 2000; 147:436–8.
van der Kooy D. Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 229–40.
Vaysse PJ-J, Gardner EL, Zukin RS. Modulation of rat brain opioid receptors by cannabinoids. J Pharmacol Exp Ther 1987;241:534–9.
Volkow ND, Wang G-J, Fowler JS, Logan J, Hitzemann RJ, Ding Y-S, et al. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcohol Clin Exp Res 1996;20:1594–8.
Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, Hitzemann RJ, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 1997;386:830–3.
Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, Gifford A, et al. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D_2 receptor levels. Am J Psychiatry 1999;156:1440–3.
Volkow ND, Chang L, Wang G-J, Fowler JS, Ding Y-S, Sedler M, et al. Low level of brain dopamine D_2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry 2001;158:2015–21.
Vorel SR, Liu X, Hayes RJ, Spector JA, Gardner EL. Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science 2001; 292:1175–8.
Walaas I, Fonnum F. Biochemical evidence for gamma-aminobutyrate containing fibres from the nucleus accumbens to the substantia nigra and ventral tegmental area in the rat. Neuroscience 1980;5:63–72.
Weeks JR, Collins RJ. Screening for drug reinforcement using intravenous self-administration in the rat. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 35–43.
Wenger T, Moldrich G, Furst S. Neuromorphological background of cannabis addiction. Brain Res Bull 2003;61:125–8.
Westerink BH, Tuntler J, Damsma G, Rollema H, de Vries JB. The use of tetrodotoxin for the characterization of drug-enhanced dopamine release in conscious rats studied by brain dialysis. Naunyn-Schmiedeberg's Arch Pharmacol 1987;336:502–7.
White NM, Hiroi N. Amphetamine conditioned cue preference and the neurobiology of drug-seeking. Semin Neurosci 1993;5:329–36.
Wickelgren I. Getting the brain's attention. Science 1997;278:35–7.
Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signaling at hippocampal synapses. Nature 2001;410:588–92.
Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science 2002;296:678–82.
Wise RA. Addictive drugs and brain stimulation reward. Annu Rev Neurosci 1996;19:319–40.
Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci 2004; 5:1–12.
Wise RA, Bozarth MA. Brain reward circuitry: four circuit elements "wired" in apparent series. Brain Res Bull 1984;12:203–8.
Wise RA, Gardner EL. Functional anatomy of substance-related disorders. In: D'haenen H, den Boer JA, Willner P, editors. Biological psychiatry. New York: Wiley; 2002. p. 509–22.
Wise RA, Gardner EL. Animal models of addiction. In: Charney DS, Nestler EJ, editors. Neurobiology of mental illness, 2nd edn. London: Oxford University Press; 2004. p. 683–97.
Wise RA, Munn E. Withdrawal from chronic amphetamine elevates baseline intracranial self-stimulation thresholds. Psychopharmacology 1995;117:130–6.

Wise RA, Murray A, Bozarth MA. Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. Psychopharmacology 1990;100:355–60.

Wolf ME. Addiction: making the connection between behavioral changes and neuronal plasticity in specific pathways. Mol Interv 2002;2:146–57.

Wood PL, Altar CA. Dopamine release in vivo from nigrostriatal, mesolimbic, and mesocortical neurons: utility of 3-methoxytyramine measurements. Pharmacol Rev 1988;40:163–87.

Woodward DJ, Chang JY, Janak P, Azarov A, Anstrom K. Mesolimbic neuronal activity across behavioral states. Ann N Y Acad Sci 1999;877:91–112.

Wu X, French ED. Effects of chronic Δ^9-tetrahydrocannabinol on rat midbrain neurons: an electrophysiological assessment. Neuropharmacology 2000;39:391–8.

Xi Z-X, Stein EA. Baclofen inhibits heroin self-administration behavior and mesolimbic dopamine release. J Pharmacol Exp Ther 1999; 290:1369–74.

Yanagita T. Prediction of drug abuse liability from animal studies. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 189–98.

Yokel RA. Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preferences. In: Bozarth MA, editor. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987. p. 1–33.