Chemistry and Physics of Lipids 121 (2002) 267–290

www.elsevier.com/locate/chemphyslip

Review

Addictive potential of cannabinoids: the underlying neurobiology

Eliot L. Gardner *

Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Building C, Room 272, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA

Received 13 September 2002; accepted 17 September 2002

Abstract

Drugs that are addictive in humans have a number of commonalities in animal model systems—(1) they enhance electrical brain-stimulation reward in the core meso-accumbens reward circuitry of the brain, a circuit encompassing that portion of the medial forebrain bundle (MFB) which links the ventral tegmental area (VTA) of the mesencephalic midbrain with the nucleus accumbens (Acb) of the ventral limbic forebrain; (2) they enhance neural firing of a core dopamine (DA) component of this meso-accumbens reward circuit; (3) they enhance DA tone in this reward-relevant meso-accumbens DA circuit, with resultant enhancement of extracellular Acb DA; (4) they produce conditioned place preference (CPP), a behavioral model of incentive motivation; (5) they are self-administered; and (6) they trigger reinstatement of drug-seeking behavior in animals behaviorally extinguished from intravenous drug self-administration behavior and, perforce, pharmacologically detoxified from their self-administered drug. Cannabinoids were long considered 'anomalous', in that they were believed to not interact with these brain reward processes or support drug-seeking and drug-taking behavior in these animal model systems. However, it is now clear—from the published data of several research groups over the last 15 years—that this view of cannabinoid action on brain reward processes and reward-related behaviors is untenable. This paper reviews those data, and concludes that cannabinoids act on brain reward processes and reward-related behaviors in strikingly similar fashion to other addictive drugs.

Keywords: Addiction; Brain stimulation reward; Cannabis; Cannabinoids; Conditioned place preference; Dopamine; Limbic; Marijuana; Medial forebrain bundle; Meso-accumbens; Mesolimbic; Microdialysis; Nucleus accumbens; Reinforcement; Reinstatement; Relapse; Reward; Self-administration; Self-stimulation; Ventral tegmental area

Abbreviations: Acb, nucleus accumbens; BLA, basolateral amygdala; BNST, bed nucleus of 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; GABA, γ-aminobutyric acid; MFB, medial forebrain bundle; MPFC, medial prefrontal cortex; 3-MT, 3-methoxytyramine; PR, progressive-ratio; THC, Δ^9-tetrahydrocannabinol; VP, ventral pallidum; VTA, ventral tegmental area.

* Tel.: +1-410-550-1634; fax: +1-410-550-1612

E-mail address: egardner@intra.nida.nih.gov (E.L. Gardner).

0009-3084/02/$ - see front matter
PII: S0009-3084(02)00162-7

1. Introduction

The reward circuitry of the mammalian brain consists of synaptically interconnected neurons which link the ventral tegmental area (VTA), nucleus accumbens (Acb), ventral pallidum (VP), and medial prefrontal cortex (MPFC). Laboratory animals avidly self-administer mild electrical stimulation to these loci, and to the medial forebrain bundle (MFB) which interconnects the VTA, Acb, and MPFC. Mild electrical stimulation of this circuit is intensely pleasurable in humans. This circuit is strongly implicated in the neural processes underlying drug addiction, and inhibition of this circuit is implicated in such phenomena as withdrawal dysphoria and dysphoria-mediated drug craving. These brain processes are believed to have evolved to subserve biologically essential natural rewards, such as the seeking and consumption of food and water, the seeking of and mating with sexual partners, and the performance of parenting behaviors. These brain processes are also believed to subserve drug-seeking and drug-taking behaviors supported by addictive drugs. Cannabinoids are euphorigenic in humans and have addictive liability, but were long considered to be devoid of pharmacological action on these brain reward processes or on drug-seeking and drug-taking behaviors. Work with cannabinoids over the last 15 years, however, makes it clear that they interact with these brain processes and influence drug-seeking and drug-taking behaviors in a manner strikingly similar to that of other addictive drugs.

2. Brain reward processes

2.1. Neuroanatomy, neurophysiology, and neurochemistry of brain reward

The neuroanatomy, neurophysiology, and neurochemistry of brain reward processes is known to involve a series of neural links associated with the MFB and located in the ventral limbic midbrain/forebrain (Gardner, 1997). Neuroanatomically, this system appears to consist of 'first-stage', 'second-stage', and 'third-stage' reward-related neurons 'in series' with one another (Wise and Bozarth, 1984; Gardner, 1997). From anatomical tracing studies and electrophysiological studies which allow inference regarding direction of neuronal conduction (Gallistel et al., 1981), it is known that the 'first-stage' neurons originate from a disparate group of ventral limbic forebrain loci termed by some neuroanatomists 'the anterior bed nuclei of the MFB' (horizontal limb of the diagonal band of Broca, olfactory tubercle, magnocellular preoptic nucleus, lateral preoptic area, interstitial nucleus of the stria medullaris, VP, substantia innominata, and anterior lateral hypothalamus). These 'first-stage' neurons are myelinated and moderately fast-conducting, and they project posteriorly through the MFB to synapse on VTA DA cells. The 'second-stage' DA neurons project anteriorly within the MFB to synapse in the Acb. Only a small subset of these DA neurons appear specialized for carrying reward-relevant information (Gardner, 1997). From Acb, 'third-stage' enkephalinergic neurons carry the reward signal to VP. This 'third-stage' pathway appears critical for expression of reward-related and incentive-related behaviors (Bardo, 1998; Napier and Mitrovic, 1999; McBride et al., 1999). The VTA, Acb, and VP are mutually interconnected by reciprocal anatomic pathways which appear to regulate reward functions and reward-driven behaviors. A portion of the 'third-stage' pathway consists of enkephalinergic Acb projection neurons which co-localize γ-aminobutyric acid (GABA) as a co-transmitter. Whether as a co-transmitter or as a solitary neurotransmitter, the GABA of the medium spiny Acb output neurons appears to play an important role in brain reward functions (Carlezon and Wise, 1996). Additional neural elements synapse onto the 'first-stage', 'second-stage', or 'third-stage' components of this brain reward system, presumably to regulate hedonic tone and other reward-related processes. These regulatory inputs include opioid peptidergic, serotonergic, GABAergic, and glutamatergic neural elements (Gardner, 1997). Recently, the GABAergic and glutamatergic neural inputs into this core reward system have come to be recognized as critically important in the regulation of reward processes and reward-driven behaviors

(Gardner, 2000; Vorel et al., 2001). From studies in which single-neuron electrophysiological recordings have been coupled with reward-related behavioral contingencies, it appears that the neurons in the core reward system are functionally heterogeneous. Some neurons seem to encode reward itself while others seem to encode 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; Schultz et al., 1997; Wickelgren, 1997; Berridge and Robinson, 1998; Everitt et al., 1999; Redgrave et al., 1999; Woodward et al., 1999). There also appears to be significant functional plasticity within these systems with respect to neural tasking and reward processing (Schultz et al., 1997; Woodward et al., 1999). Even with such functional heterogeneity and plasticity, one of the primary functions of these reward processes is to compute hedonic tone and neural 'payoffs' (Kornetsky and Bain, 1992; Kornetsky and Duvauchelle, 1994; Shizgal, 1997; Peoples et al., 1999). As noted above, these brain processes presumably evolved to subserve natural, biologically significant rewards (Goldstein, 2001).

2.2. Addictive drug action on brain reward processes

Addictive drugs activate the above-referenced brain reward processes. Such drugs appear to activate the 'second-stage' DA neurons of the VTA–Acb axis, thus, producing the pleasurable/euphoric effects that constitute the 'high', 'rush', or 'blast' (Simon and Burns, 1997) sought by drug addicts. For some addictive drugs (e.g. amphetamines, cocaine), the action on the VTA–Acb DA neurons appears to be direct. For other addictive drugs (e.g. opiates), the action on the VTA–Acb DA neurons appears to be indirect or even transsynaptic (Gardner, 1997). The DA component appears to be a crucial common substrate upon which addictive drugs (regardless of chemical structure or pharmacological category) act to enhance brain reward processes—and, thus, to enhance both the subjective experience of reward and reward-related behaviors. Drug reward by itself and drug potentiation of electrical brain stimulation reward (BSR) appear to have common actions within these reward substrates (Wise, 1996). BSR and the pharmacological reward produced by addictive drugs are both more powerful and immediate than the reward produced by natural, biologically essential reinforcers (Goldstein, 2001). Addictive drugs appear to gain their habit-forming power by 'hijacking' the reward substrates that originally evolved to subserve natural rewards and activating them more powerfully than natural rewards (Goldstein, 2001).

2.3. Brain reward dysregulation as a cause of addiction

That addictive drugs activate brain reward processes seems clear (Gardner, 1997), as does the inference that this activation produces the subjective 'high' or 'rush' or 'blast' that drug users seek (Simon and Burns, 1997). What is not clear is why some people can use addictive drugs on an occasional recreational basis, while other users deteriorate into a self-destructive, obsessional, compulsive, and addictive pattern of use. Genetic factors are believed to play an important role (Uhl et al., 1993). At the animal level, genetic factors are clearly involved in proclivity to self-administer addictive drugs, and in the ease with which initially neutral environmental cues can acquire positive incentive salience as a result of being paired with addictive drugs (George and Goldberg, 1989; Suzuki et al., 1989; Guitart et al., 1992; Kosten et al., 1997). At the cellular and molecular level, genetic vulnerability to addictive drugs correlates with decreased neurofilamentary transport for tyrosine hydroxylase (the rate-limiting intraneuronal DA synthetic enzyme) in VTA–Acb DA reward-related neurons (Nestler, 1993; Self and Nestler, 1995). This produces a DA deficiency in these VTA–Acb brain reward neurons which is hypothesized to underlie vulnerability to addictive drug action (Blum et al., 1996a; Gardner, 1999). Another type of DA dysfunction in the VTA–Acb brain reward axis which has been hypothesized to underlie vulnerability to addictive drugs centers on a deficiency in DA D2 receptors. 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., 1996b). Recently, this hypothesis has been supported by human neuroimaging findings of lower DA D2 receptor levels in brain reward loci of drug addicts (Volkow et al., 1996, 1997, 2001), by findings that low levels of DA D2 receptors in human brain reward loci predict reinforcing versus non-reinforcing subjective responses to psychostimulants (Volkow et al., 1999), and by animal studies in which overexpression of DA D2 receptors decreases self-administration of addictive drugs (e.g. Thanos et al., 2001). A more complex explanatory scheme of the cellular neurobiological processes underlying both initial vulnerability and relapse to drug addiction, involving a cascade of homeostatic dysregulations within both the brain's VTA–Acb reward processes and in circuits interconnecting with these reward processes, has also been advanced (Koob and Le Moal, 1997; Koob, 1999). In this view, increased vulnerability to drug abuse conferred by genetic factors, drug use, or withdrawal dysphoria is conceived to involve decreased VTA–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. Modeling addiction with animal behavioral models

A number of salient features of addictive behavior at the human level have been successfully modeled at the animal level, with seemingly good face validity and predictive validity to the human situation (Gardner, 2000; Wise and Gardner, 2002a). These models include conditioned place preference (CPP), drug self-administration, and reinstatement.

3.1.1. Conditioned place preference

The CPP paradigm is used to study drug-seeking behavior, and to infer the incentive motivational value and strength of addictive drugs (Mucha et al., 1982; Schechter and Calcagnetti, 1993; Tzschentke, 1998). Basically, this procedure reflects the ability of neutral environmental cues or contexts to acquire incentive salience (Bindra, 1968; Robinson and Berridge, 1993) by repeated pairing with addictive drugs. During training, animals are given drug injections and then confined to one part of the test apparatus (containing distinct visual, tactile, and/or olfactory cues) on some days and given vehicle injections then confined to another part of the test apparatus (containing distinctively different visual, tactile, and/or olfactory cues) on other days. On test days the animals are given free choice between the two regions of the test apparatus and the time spent in each region is measured. Drug-induced reward is inferred from an increase in the time spent in the drug-associated portion of the environment.

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. Laboratory animals will self-administer several classes of addictive drugs by the oral, intragastric, intraperitoneal, intravenous, or even intracranial routes and will do so in the absence of physical dependence (Bozarth and Wise, 1984; Gardner, 1997, 2000). In the strongest version of the model, the animal is required to work for access to the drug and not merely to ingest it. While this model is most often used with fixed-ratio reinforcement contingencies (e.g. one intravenous injection of drug given for one unit of work performed by the animal), an interesting variant is one 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 a drug injection. For example, the work-load may

literally increase in ratio fashion: one lever-press required for the first injection, two for the second injection, four for the third, eight for the fourth, etc. Although typically the work-load is not increased so steeply, in every PR drug self-administration test session a point is reached at which the animal's responding falls below some criterion level (often, an abrupt cessation of responding)—the so-called PR 'break-point'. This 'break-point' is taken as a measure of the drug's rewarding efficacy. Compellingly, PR 'break-point' estimates of the rewarding efficacies of addictive drugs in animals closely parallel verbal rank orderings of appetitiveness of addictive drugs given by experienced poly-drug abusing humans (Gardner, 2000). This adds credence to the contention that the self-administration paradigm is a valid animal model of human drug addiction.

3.1.3. Reinstatement

The 'reinstatement' variant of the drug self-administration paradigm is used to study relapse to drug-seeking and drug-taking behavior. In this paradigm the animal is trained to self-administer a drug, usually intravenously, to a satisfactorily stable level of drug-taking. The animal is then subjected to behavioral extinction of the drug-taking habit. That is, the animal is tested under conditions of non-reinforcement until the drug-taking habit disappears (to an operationally defined criterion). When the animal reaches the defined criterion of non-drug-seeking, various external stimuli are used to provoke relapse to the drug-seeking behavior. A stimulus is said to 'reinstate' the drug-seeking habit if it causes renewed responding despite the absence of any further response-contingent drug reward. Three types of external stimuli have been found to provoke relapse in this model—a single non-contingent 'priming' administration of drug (de Wit and Stewart, 1981, 1983; Stewart and de Wit, 1987), stress (Shaham and Stewart, 1995; Erb et al., 1996; Shaham et al., 1996), or environmental stimuli 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 DA appear to be essential substrates for drug-triggered relapse in the reinstatement paradigm (Grimm and See, 2000; Shalev et al., 2002). The basolateral amygdala (BLA) and the neurotransmitter glutamate appear to be essential substrates for cue-triggered relapse in the reinstatement paradigm (Grimm and See, 2000; Hayes et al., 2002). The CeA, bed nucleus of stria terminalis (BNST), lateral tegmental noradrenergic projection system, and the CRF projection pathway from the CeA to the BNST appear to be essential substrates for stress-triggered relapse in the reinstatement paradigm (Shalev et al., 2002). Especially compelling is the fact that cross-priming (from one class of addictive drug to another) is seen in this model. Thus, priming doses of opiates trigger relapse to cocaine self-administration behavior (Stewart, 1984) and priming doses of amphetamine or the DA agonist bromocriptine trigger relapse to opiate self-administration behavior (Stewart and Vezina, 1988; Wise et al., 1990). Very importantly, only drugs which support drug-seeking and drug-taking behaviors can 'prime' or trigger relapse in the reinstatement paradigm. The drugs and doses which trigger relapse to drug-seeking and drug-taking in both humans and animals are drugs and doses which increase DA function within the mesoaccumbens DA reward system (Stewart and Vezina, 1988; Wise et al., 1990).

3.2. Addictive drug action on reward-related behaviors

Addictive drugs constitute a remarkably small fraction of the total number of known chemicals. Only a few score are addictive at the human level or capable of supporting drug-seeking and drug-taking at the laboratory animal level (Griffiths et al., 1978; Brady and Lucas, 1984; Yokel, 1987). Since addictive drugs as a class have neither chemical commonality nor classical pharmacological commonality, the following questions arise: (a) what do addictive drugs have in common?, and (b) what distinguishes them from the millions of other drugs lacking addictive liability? The answers at the animal behavioral level are three-fold: (a) with few exceptions, addictive drugs support CPP (Mucha et al., 1982; Schechter and Calcag-

netti, 1993; Tzschentke, 1998; Wise and Gardner, 2002a); (b) almost without exception, drugs that are addictive at the human level support voluntary self-administration by laboratory animals, and the same drugs that are eschewed by humans are eschewed by 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, 2002a) and (c) to the extent that they have been studied in the reinstatement paradigm, 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, 2002a).

4. Cannabinoid effects on brain reward processes

Although cannabinoids have clear addictive potential at the human level (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), they have been labeled by some (e.g. Felder and Glass, 1998) as 'anomalous', i.e. having no action on brain reward processes. Simply stated, this is an untenable position. Over the last 15 years, a large body of research has made it clear that marijuana and other cannabinoids act on the above-outlined brain reward processes in strikingly similar fashion to non-cannabinoid addictive drugs.

4.1. Cannabinoid effects on electrical BSR

Δ^9-Tetrahydrocannabinol (THC), the psychoactive and addictive constituent of marijuana and hashish, enhances electrical BSR (i.e. lowers brain-reward thresholds) in the VTA–Acb reward axis in laboratory animals (see Fig. 1; Gardner et al., 1988a; Gardner and Lowinson, 1991; Gardner, 1992; Gardner et al., 1995; Lepore et al., 1996). This is seen with both an auto-titration quantitative electrophysiological reward-threshold measurement paradigm and a rate-frequency curve-shift quantitative electrophysiological reward-threshold measurement paradigm. In the auto-titration paradigm (Gardner et al., 1988a), animals are studied in test chambers containing two response levers. Each response by the animal on the primary or 'stimulation' lever delivers BSR, the initial intensity of which is optimized for each animal at a clearly supra-threshold reward level (in μA), and decreases by a fixed amount at every third press of the primary lever. The animal can reset the current back to the initial intensity maximum at any time by pressing a 'reset' lever (which does not deliver BSR, but simply resets the stimulus strength). The mean self-determined reset level is taken as the animal's self-chosen reward threshold (below which the animal feels no subjective reward). In the rate-frequency curve-shift paradigm, (Gardner et al., 1995; Lepore et al., 1996), animals are trained to lever-press for a series of 16 different rewarding electrical pulse frequencies, ranging from 25 to 141 Hz, presented in descending order. The initial frequency is optimized for each animal at a clearly supra-threshold reward level. At each pulse frequency, animals are given the opportunity to lever-press for rewarding electrical BSR for two 30-s time periods ('bins'), following which the pulse frequency decreases by 0.05 log units. Two measures of reward threshold are taken: M_{50}—the pulse frequency at which the animal lever-presses at half-maximum speed; and Θ_0—the frequency at which the animal ceases to respond for BSR. Both are reliable indices of reward efficacy. Using either BSR paradigm, THC at low doses (e.g. 1.0 mg/kg) reliably and robustly lowers brain reward thresholds, i.e. enhances brain reward processes (Gardner et al., 1988a; Gardner and Lowinson, 1991; Gardner, 1992; Gardner et al., 1995; Lepore et al., 1996).

4.2. Cannabinoid effects on DA neuronal firing in brain reward circuitry

Addictive drugs enhance DA function in brain reward loci by several means. Some, such as cocaine and amphetamines, accomplish this by enhancing DA release or inhibiting DA reuptake (Gardner, 1997). Others, such as nicotine and

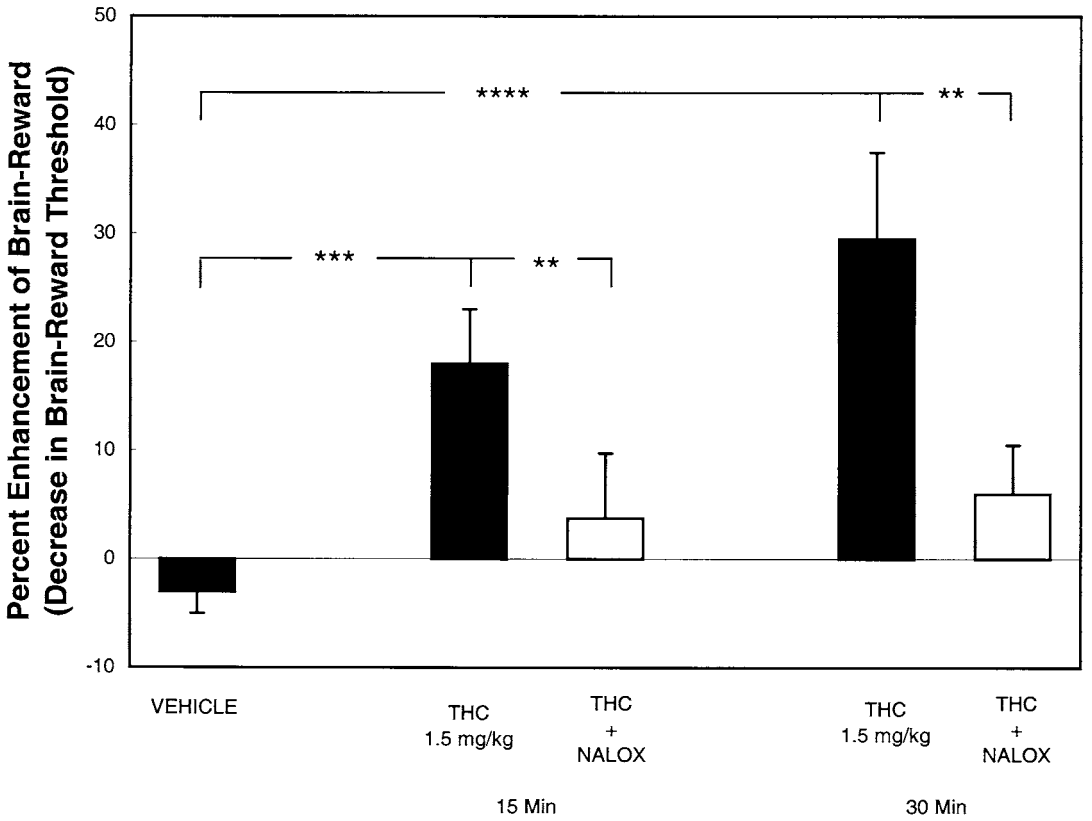

Fig. 1. Cannabinoid-induced enhancement of brain-reward, and attenuation of cannabinoid-induced brain-reward enhancement by the opioid antagonist naloxone (see text). THC, Δ^9-tetrahydrocannabinol. NALOX, naloxone. Asterisks indicate statistical significance levels for the comparisons indicated: **, $P < 0.01$; ***, $P < 0.005$; ****, $P < 0.001$.

opioids, accomplish this by stimulating the firing rate of the 'second-stage' reward-relevant DA neurons (Gysling and Wang, 1983; Grenhoff et al., 1986; Gardner, 1997). In vivo single-neuron electrophysiological recording techniques have been used to assess whether cannabinoids augment DA function in the reward system by enhancing DA neuronal firing (Melis et al., 1996; French, 1997; French et al., 1997; Gifford et al., 1997; Diana et al., 1998a; Gessa et al., 1998). The preponderance of evidence from these studies 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). The effect is seen in VTA–Acb DA neurons, and also in the adjacent nigro-striatal and meso-prefrontal DA neurons. The enhanced DA firing is more pronounced in the VTA–Acb DA axis than in other forebrain DA loci (French et al., 1997). This is congruent with the known preferential action of other addictive drugs on DA neurons of the VTA–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), although not by the opiate antagonist naloxone (French, 1997). This is highly provocative as to mechanisms of cannabinoid activation of brain reward processes, as naloxone does significantly attenuate cannabinoid-induced elevations of Acb DA (see below). In some meso-prefrontal DA neurons, cannabinoid administration does not increase firing rate, but rather produces an increase in

neuronal bursting activity (Diana et al., 1998a). This is also provocative, as it is known that the burst-firing state of mesotelencephalic DA neurons produces dramatically increased (supra-additive) DA release at axon terminals (Gonon, 1988; Overton and Clark, 1997).

4.3. Cannabinoid effects on DA neurochemical substrates of brain reward

4.3.1. In vitro studies

THC enhances DA synthesis, as studied by in vitro assay systems (Bloom, 1982; Navarro et al., 1993). 9-Nor-9beta-hydroxyhexahydrocannabinol, a potent antinociceptive cannabinoid, shares this feature (Bloom et al., 1977). THC also inhibits DA neuronal uptake, as studied by in vitro assay systems (Banerjee et al., 1975; Johnson et al., 1976; Hershkowitz et al., 1977; Poddar and Dewey, 1980). However, the picture is much less clear concerning cannabinoid effects on DA release, as studied by in vitro assay systems. Cannabinoid-induced enhancement (Poddar and Dewey, 1980; Jentsch et al., 1998), no effect (Szabo et al., 1999), and cannabinoid-induced inhibition (Cadogan et al., 1997) of neuronal DA release have all been reported.

4.3.2. In vivo studies

More than 15 years ago, cannabinoid-induced enhancement of extracellular DA overflow in brain reward loci, as measured by in vivo brain microdialysis in awake behaving animals, was reported (Ng Cheong Ton and Gardner, 1986). Subsequent work (Ng Cheong Ton et al., 1988; Taylor et al., 1988; Chen et al., 1989, 1990a,b; Tanda et al., 1997; Malone and Taylor, 1999) has amply confirmed those original reports (see Fig. 2). The 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). This DA-enhancing effect is also seen with the synthetic cannabinoid agonist WIN-55212-2, and is blocked by the selective cannabinoid antagonist SR-141716A (Tanda et al., 1997). Cannabinoid-induced DA enhancement is seen not only in Acb (Chen et al., 1990b) but also in other reward-related forebrain DA terminal loci, including MPFC (Chen et al., 1990a) and neostriatum (Ng Cheong Ton and Gardner, 1986; Ng Cheong Ton et al., 1988; Taylor et al., 1988; Malone and Taylor, 1999). Within the Acb, THC's DA-enhancing effect occurs selectively within the Acb shell (Tanda et al., 1997). This is congruent with a large literature implicating the shell as the anatomic domain within Acb most specialized for mediating drug-enhanced brain reward (Johnson et al., 1995; Pontieri et al., 1995; Carlezon and Wise, 1996; Gardner, 1997; McBride et al., 1999). Also more than 15 years ago, confirmatory findings of cannabinoid-induced enhancement of extracellular DA overflow in reward-relevant brain loci using in vivo brain voltammetric electrochemistry were published (Ng Cheong Ton et al., 1988; Gardner and Lowinson, 1991). Thus, despite one negative report (Castañeda et al., 1991), the overwhelming evidence from several different labs and using two different in vivo neurochemical techniques is that cannabinoids enhance extracellular DA in forebrain reward loci.

4.4. Genetic variation in cannabinoid actions on brain reward processes

Genetic differences exist in preference for specific addictive drugs and in propensity to self-administer such drugs (Cannon and Carrell, 1987; George, 1987; George and Goldberg, 1989; Suzuki et al., 1989; Guitart et al., 1992; Kosten et al., 1994, 1997; Nestler, 1993). Some animal strains which show high ethanol preference and self-administration generalize this drug-seeking behavior to other addictive drugs such as nicotine and opiates (George and Meisch, 1984; Khodzhagel'diev, 1986; George, 1987; George and Goldberg, 1989), suggesting that generalized vulnerability to the rewarding effects of addictive drugs is genetically influenced. The Lewis rat strain is particularly interesting. As compared to other rat strains, Lewis rats are inherently drug-seeking and drug-preferring. They work harder for opiate and cocaine self-administration, cue-condition more readily to opiates and cocaine, and voluntarily drink ethanol more readily (George and Goldberg, 1989; Suzuki et al., 1989; Guitart et

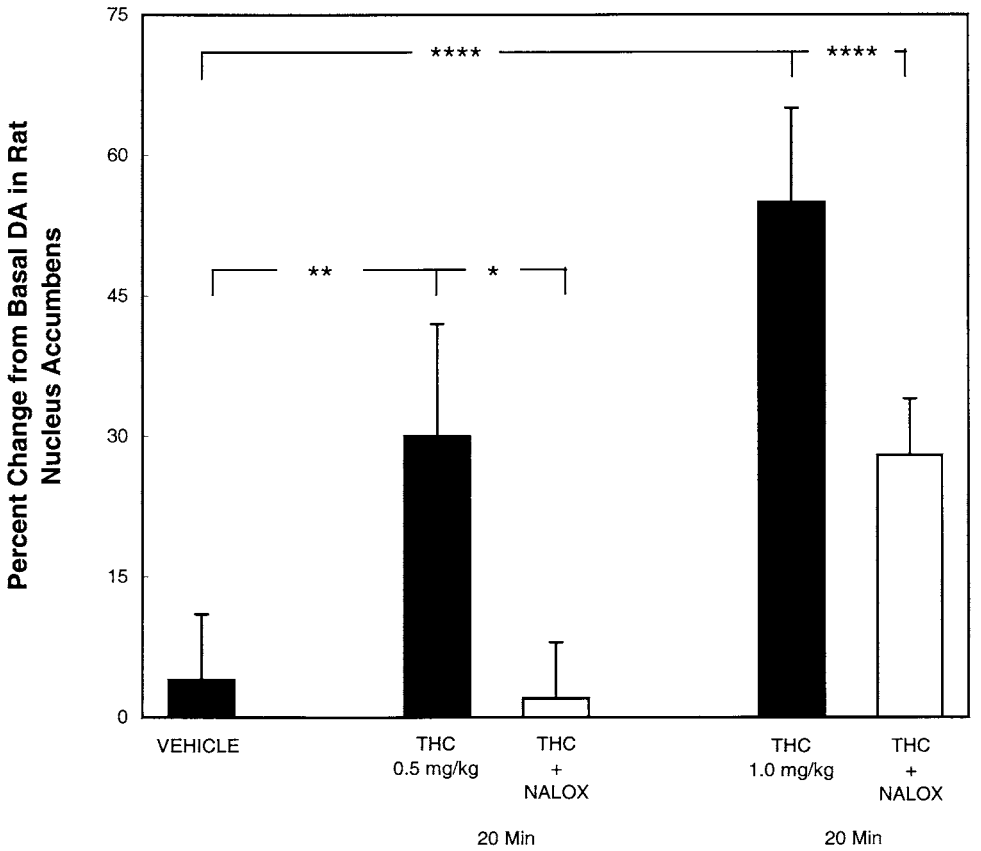

Fig. 2. Cannabinoid-induced enhancement of extracellular DA overflow in the reward-related DA axon terminal-rich Acb, and attenuation of cannabinoid-induced enhancement of extracellular Acb DA by the opioid antagonist naloxone (see text). THC, Δ^9-tetrahydrocannabinol. NALOX, naloxone. Asterisks indicate statistical significance levels for the comparisons indicated: *, $P < 0.05$; **, $P < 0.01$; ****, $P < 0.001$.

al., 1992; Misenrendino et al., 1992; Nestler, 1993). Do cannabinoid effects on brain reward processes show similar genetic variation? To answer this question, cannabinoid effects on brain reward have been studied in various rat strains. Using quantitative electrophysiological BSR techniques, THC has been found to produce robust BSR enhancement in drug-preferring Lewis rats, moderate enhancement in drug-neutral Sprague–Dawley rats, and no change in drug-resistant Fischer 344 rats (see Fig. 3; Gardner et al., 1988b, 1989a, 1995; Lepore et al., 1996). Using in vivo brain microdialysis, THC has been found to produce robust enhancement of Acb DA in drug-preferring Lewis rats, moderate enhancement in drug-neutral Sprague-Dawley rats, and no change in drug-resistant Fischer 344 rats (see Fig. 4; Gardner et al., 1989a; Chen et al., 1991).

4.5. Cannabinoid withdrawal and brain reward processes

As noted above, addictive drugs enhance BSR and augment DA in brain reward loci. As noted, this is a distinguishing pharmacological characteristic of addictive drugs. Conversely, withdrawal from addictive drugs produces inhibition of BSR and depletion of DA in brain reward loci (Schaefer and Michael, 1986; Frank et al., 1988; Schulteis et al., 1994; Wise and Munn, 1995; Parsons et al., 1991; Pothos et al., 1991; Rossetti et al., 1992). These withdrawal effects on brain reward pro-

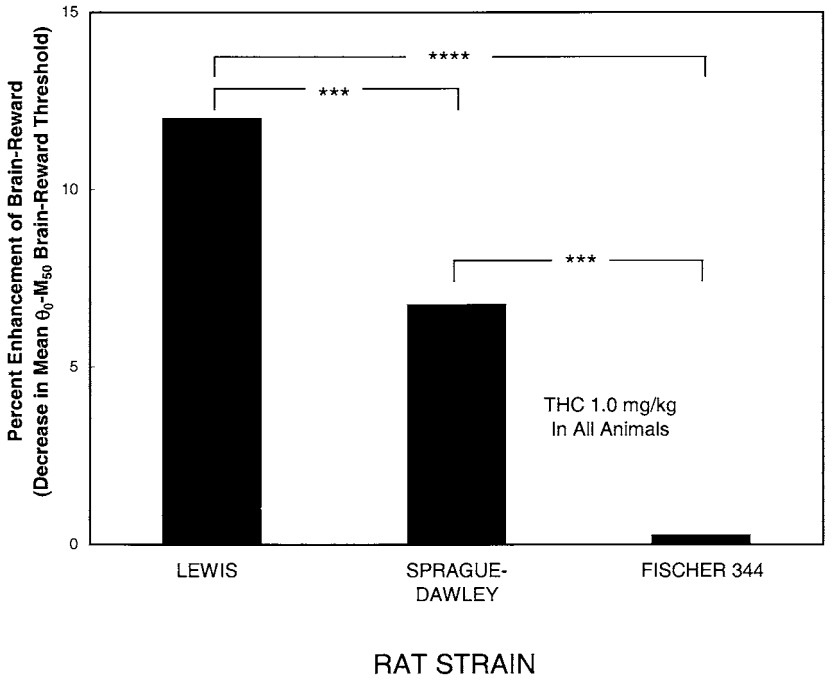

Fig. 3. Genetic variation in cannabinoid-induced enhancement of brain-reward (see text). THC, Δ^9-tetrahydrocannabinol. Asterisks indicate statistical significance levels for the comparisons indicated: ***, $P < 0.005$; ****, $P < 0.001$.

cesses are also a distinguishing pharmacological characteristic of addictive drugs. The question, thus, arises—does cannabinoid withdrawal mimic withdrawal from other addicting drugs, either with respect to BSR thresholds or DA function in the VTA–Acb reward axis? The answer seems clear. Withdrawal from as little as a single 1.0 mg/kg dose of THC produces significant BSR inhibition (see Fig. 5; Gardner and Vorel, 1998), identical to that seen in withdrawal from other addictive drugs. With respect to DA function within the VTA–Acb neural reward axis, withdrawal from chronic THC—precipitated either by abrupt THC discontinuance or by the selective CB1 cannabinoid receptor antagonist SR-141716A, produces a reduction in VTA–Acb DA neuronal cell activity (reversed by the administration of THC in the case of the discontinuance-precipitated withdrawal) (Diana et al., 1998b) and a reduction of in vivo microdialysate-measured DA in the Acb shell (Tanda et al., 1999). Thus, cannabinoid withdrawal is characterized by reduced DA transmission in the VTA–Acb reward axis, similar to that seen during withdrawal from other addictive drugs, a pharmacological hallmark of addictive drugs. Another common feature of withdrawal from addictive drugs is CRF elevation in the CeA (Koob et al., 1993; Merlo Pich et al., 1995; Koob, 1996). This is provocative, as the amygdala is increasingly implicated in mediating the functions of 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., 2002). Does cannabinoid withdrawal mimic withdrawal from other addictive drugs in this regard? Recent reports suggest strongly that it does. Cannabinoid withdrawal is accompanied by marked elevation in extracellular CeA CRF (Rodríguez de Fonseca et al., 1997), similar to that seen in withdrawal from other addictive drugs. Thus, cannabinoid withdrawal mimics withdrawal from other addictive drugs with respect to effects in the two main brain systems believed to subserve initial drug-taking behavior and relapse (Koob, 1999).

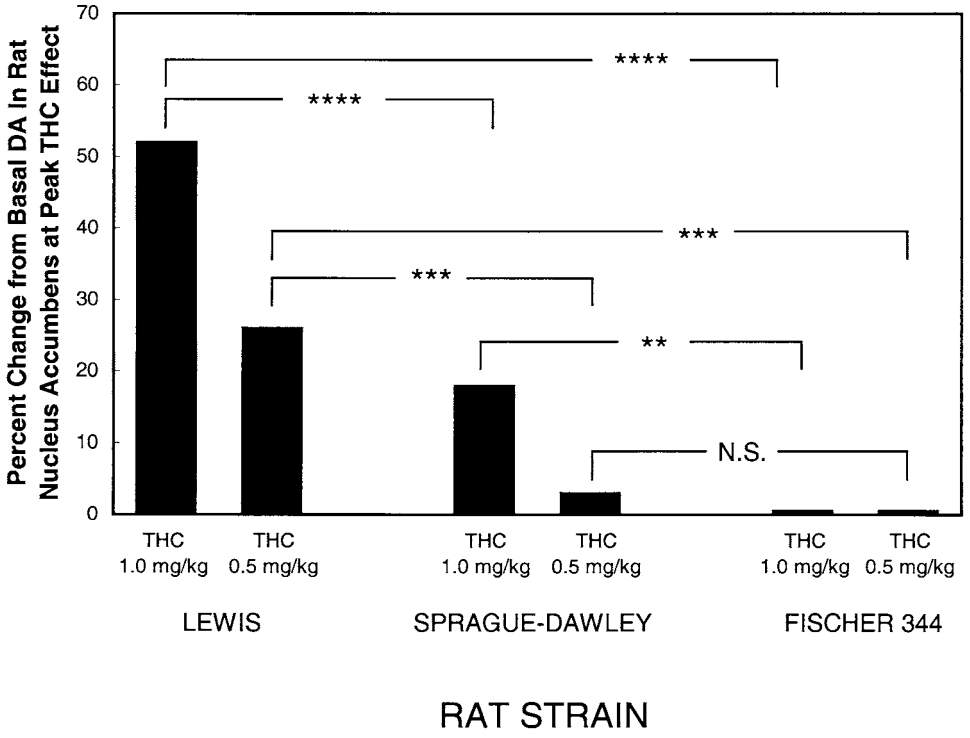

Fig. 4. Genetic variation in cannabinoid-induced enhancement of extracellular DA overflow in the reward-related DA axon terminal-rich Acb (see text). THC, Δ^9-tetrahydrocannabinol. Asterisks indicate statistical significance levels for the comparisons indicated: N.S., not significant; **, $P < 0.01$; ***, $P < 0.005$; ****, $P < 0.001$.

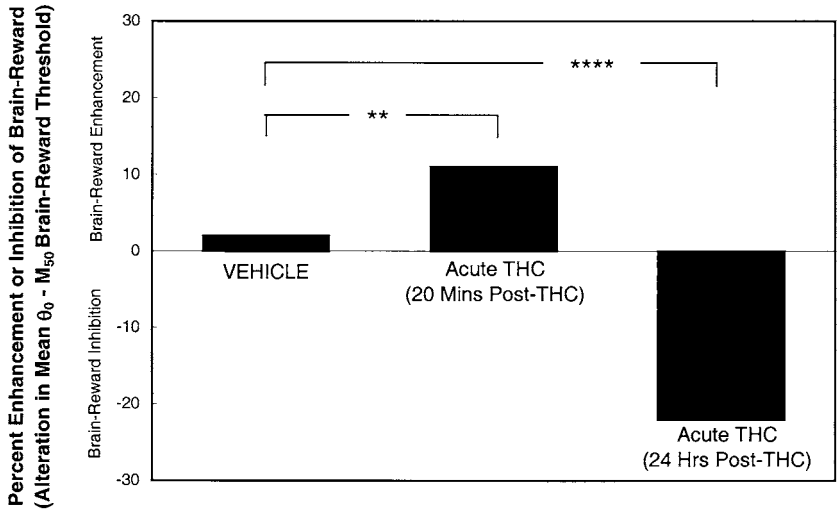

Fig. 5. Enhancement of brain-reward by acute cannabinoid administration, and inhibition of brain-reward during withdrawal from acute cannabinoid administration (see text). THC, Δ^9-tetrahydrocannabinol. Asterisks indicate statistical significance levels for the comparisons indicated: **, $P < 0.01$; ****, $P < 0.001$.

4.6. Endogenous opioid involvement in cannabinoid actions on brain reward processes

Yet another distinguishing feature of addictive drug action on brain reward processes is the involvement of endogenous opioid systems, even for non-opioid addictive drugs (Gardner, 1997, 2000). The core DA brain reward axis is anatomically and functionally interconnected with endogenous brain opioid peptide neural systems in the VTA, Acb, and VP (Gardner, 1997). These endogenous opioid peptide systems appear importantly involved in the set-point of hedonic tone, and in the expression of reward-related and incentive-related behaviors (Gardner, 2000). The enhanced brain reward produced by addictive drugs (including non-opiates such as ethanol, barbiturates, benzodiazepines, phencyclidine, amphetamines and cocaine) is blocked or attenuated by opiate antagonists (Gardner, 1997). This implicates endogenous opioid peptidergic mechanisms in mediating the rewarding actions of such drugs. It also provides yet another distinctive neurobiological 'signature' of addictive drug action. The question therefore arises—are cannabinoid effects on brain reward systems similarly blocked or attenuated by opiate antagonists? This question has been addressed using BSR and in vivo brain microdialysis. With respect to BSR, the opiate antagonist naloxone attenuates THC-induced BSR enhancement (see Fig. 1; Gardner et al., 1989b; Gardner and Lowinson, 1991; Gardner, 1992). Naloxone also attenuates THC-induced enhancement of Acb DA (see Fig. 2; 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 mimics the naloxone effect (Tanda et al., 1997), implicating the μ_1 opiate receptor subtype in mediating cannabinoid effects on brain reward. These findings using in vivo brain microdialysis are congruent with an older report that naloxone attenuates THC-enhanced DA synthesis in brain, as measured by in vitro biochemistry (Bloom and Dewey, 1978). The neural mechanism underlying this attenuating effect of opiate antagonists on cannabinoid-enhanced brain reward is unknown. Of possible relevance to this question is the fact that cannabinoid and opioid receptors are both coupled to similar postsynaptic intracellular signaling mechanisms, involving activation of G_i proteins and consequent inhibition of adenylyl cyclase and decreased cAMP production (Childers et al., 1992). Also, CB1 cannabinoid receptors are co-localized with μ opioid receptors in the Acb (Navarro et al., 1998), and it has been suggested that cannabinoids and opioids may interact at the level of their signal transduction mechanisms (Thorat and Bhargava, 1994). Additionally, brain opioid receptors are modulated by cannabinoid administration (Vaysse et al., 1987) and brain cannabinoid receptors are modulated by opiate administration (Rubino et al., 1997). It is noteworthy that opiate antagonism attenuates cannabinoid effects on BSR (Gardner et al., 1989b; Gardner and Lowinson, 1991; Gardner, 1992) and on Acb DA (Chen et al., 1989, 1990b; Gardner et al., 1989b, 1990a; Gardner and Lowinson, 1991; Gardner, 1992; Tanda et al., 1997), but does not alter cannabinoid-induced increases in the firing rates of VTA–Acb DA neurons (French, 1997; Gessa and Diana, 2000). This seemingly puzzling discrepancy may have important implications for underlying neural processes (see below).

5. Cannabinoid actions on reward-related behaviors

5.1. Cannabinoid actions on CPP

As noted above, CPP is a widely used behavioral model for studying drug-seeking behavior, and inferring the incentive motivational value and strength of addictive drugs. Fundamentally, CPP is the learned approach to a previously neutral set of environmental stimuli which have been paired with administration of a rewarding treatment (van der Kooy, 1987; Tzschentke, 1998). When used to assess drug-induced reward, animals are given drug injections while confined in one of two cue-distinctive chambers and vehicle injections while confined in the other. Prior to injections, both chambers are tested to ensure their neutrality (i.e. animals voluntarily spending equal time in each). After drug injections, if the animal shows a marked preference for the drug-paired chamber,

the drug is considered to have been rewarding. If the animal avoids the drug-paired chamber, the drug is considered to have been aversive. CPP has been used by several research groups to assess the rewarding or aversive properties of cannabinoids. Some researchers 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., 2000). Another group, using cue preference/aversion rather than CPP/CPA, also reported cannabinoid-induced aversion (Goett and Kay, 1981). On the other hand, 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 related to cannabinoid dose (Lepore et al., 1995), timing (Lepore et al., 1995; Valjent and Maldonado, 2000), and potency (Braida et al., 2001a). Crucially, 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 (Lepore et al., 1995). Seemingly, 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 a 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 into an aversive dose range. Such dose-dependent switches from reward to aversion (low dose—reward; high dose—aversion) have been long recognized for other addictive drugs (Fudala et al., 1985; Jorenby et al., 1990; Gardner, 1992), and it has also been long recognized that timing of drug administration during place conditioning is as strong a determinant of CPP or CPA as the drug itself (Fudala and Iwamoto, 1990). At the human level, a parallel finding has long been noted, i.e. that low-to-moderate THC doses produce a subjective 'high' but higher doses are aversive (Noyes et al., 1975; Raft et al., 1977; Laszlo et al., 1981). Valjent and Maldonado (2000) also found timing to be crucial in the establishment of cannabinoid-induced CPP. In their hands, THC produced a clear and robust CPP when a long conditioning period was used and when care was taken to avoid dysphoric rebound from prior THC administrations (Valjent and Maldonado, 2000). In the work of Braida and colleagues, the use of the potent synthetic cannabinoid CP-55940 produced a robust CPP (Braida et al., 2001a). Compellingly, given the attenuation of cannabinoid-induced effects in other reward paradigms by opiate antagonists (see above), CP-55940's induction of CPP was fully antagonized by naloxone (Braida et al., 2001a).

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

5.2. *Cannabinoid self-administration in animal models*

Until recently, the cannabinoid literature was marked by failure to demonstrate reliable cannabinoid self-administration in laboratory animals (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). In the older literature, the few reported instances of cannabinoid self-administration in animals were methodologically problematic, i.e.: (1) cannabinoid self-administration in monkeys being contingent upon prior self-administration of other highly rewarding drugs (Pickens et al., 1973); (2) cannabinoid self-administration in monkeys being contingent upon prior cannabinoid physical dependence (Deneau and Kaymakçalan, 1971; Kaymakçalan, 1972); or (3) cannabinoid self-administration being contingent upon food deprivation (Takahashi and Singer, 1979, 1980).

Recently, however, several groups have independently reported cannabinoid self-administra-

tion in laboratory animals under methodologically cleaner conditions. Robust and consistent intravenous self-administration of the potent synthetic cannabinoid agonist WIN-55212-2 in drug-naive mice has been reported (Fratta et al., 1997; Martellotta et al., 1998; Ledent et al., 1999). This cannabinoid self-administration was blocked by the selective CB1 antagonist SR-141716A (Fratta et al., 1997; Martellotta et al., 1998). The potent synthetic cannabinoid agonist CP-55940 has also recently been reported to sustain clear and robust intracerebroventricular self-administration in laboratory rats (Braida et al., 2001b). Again, this cannabinoid self-administration was blocked by the selective CB1 antagonist SR-141716A. Compellingly, the cannabinoid self-administration was also blocked by the opiate antagonist naloxone (Braida et al., 2001b). Perhaps most compellingly of all, persistent high rates of low-dose intravenous THC self-administration in squirrel monkeys have been recently reported (Tanda et al., 2000). The THC self-administration was blocked by the selective CB1 antagonist SR-141716A (Tanda et al., 2000) and the opiate antagonist naltrexone (Goldberg et al., 2001). What makes this last report so compelling is that the doses of THC which were self-administered are comparable to doses found in marijuana smoke inhaled by human users (Tanda et al., 2000), and are from 5000 to 25000-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).

5.3. Cannabinoid actions on reinstatement

As noted above, the reinstatement model of relapse to drug-seeking behavior is uniquely responsive to drugs with addictive properties. Only drugs which support drug-seeking and drug-taking behaviors can 'prime' or trigger relapse in the reinstatement model. Little work has been done with cannabinoids in this model. However, the work done is highly suggestive of cannabinoids fitting the same pattern as other addictive drugs in this model. Specifically, systemic injections of the synthetic cannabinoid receptor agonist HU-210 dose-dependently reinstate cocaine-seeking behavior in laboratory rats behaviorally extinguished from intravenous cocaine self-administration (De Vries et al., 2001). Systemic injections of HU-210 also reinstate heroin-seeking behavior in laboratory rats behaviorally extinguished from intravenous heroin self-administration (De Vries et al., 2001). Provocatively, these same investigators found that the CB1 cannabinoid receptor antagonist SR-141716A blocked reinstatement to drug-seeking behavior triggered by cocaine, heroin, or cocaine-associated environmental cues, but not relapse induced by exposure to stress, suggesting a potential role for cannabinoid antagonists in the treatment of addiction.

6. Neural models of cannabinoid actions on brain reward processes

From the evidence cited above, and from additional available data, hypotheses may be generated regarding where and how cannabinoids act to alter brain reward processes, and in turn, reward-related behaviors.

6.1. Neural sites of cannabinoid action on brain reward

Different addictive drugs enhance brain reward processes by acting at different anatomic sites within the brain's reward circuitry (Gardner, 1997; Wise and Gardner, 2002b). Drugs deriving their addictive potential from actions within the Acb include amphetamines, cocaine, opiates, and dissociative anesthetics such as phencyclidine (Wise and Gardner, 2002b). Suggestive but substantially less solid evidence supports a speculative identification of Acb as a site of action for ethanol and caffeine (Wise and Gardner, 2002b). Drugs deriving their addictive potential from actions within the VTA include ethanol, opiates, and nicotine (Wise and Gardner, 2002b). Suggestive but substantially less solid evidence supports an identification of VTA as a site of action for barbiturates and benzodiazepines (Wise and Gardner, 2002b). Cocaine and phencyclidine appear to affect brain reward processes by actions within the

MPFC (Wise and Gardner, 2002b). In addition to their rewarding actions within Acb and VTA, opiates appear to additionally affect brain reward processes by action within the VP (Gardner, 1997).

The question arises as to the brain sites of cannabinoid action on brain reward processes. This has been addressed in several ways—both direct and inferential.

One direct way to address this question is to assess the effects of cannabinoids on the neuronal activity of the DA cells that comprise the VTA–Acb DA reward axis. As noted above, this has been done (Melis et al., 1996; French, 1997; French et al., 1997; Gifford et al., 1997; Diana et al., 1998a; Gessa et al., 1998). As noted, a strong majority of these studies indicate that cannabinoids enhance neuronal firing of DA neurons in the VTA–Acb reward axis (Melis et al., 1996; French, 1997; French et al., 1997; Diana et al., 1998a; Gessa et al., 1998). The straightforward conclusion from these studies would be that cannabinoids act on the VTA–Acb reward axis by a mechanism within the VTA, possibly by inhibition of local inhibitory GABAergic input into the VTA (French et al., 1997; Diana et al., 1998a; Gessa et al., 1998). However, this straightforward interpretation cannot be the full answer, because while cannabinoid-induced enhancement of VTA–Acb neuronal firing is attenuated by the selective CB1 cannabinoid receptor antagonist SR-141716A (French, 1997; French et al., 1997; Diana et al., 1998a) it is not attenuated (French, 1997) by doses of the opiate antagonist naloxone generally considered high enough to block endogenous opioid mechanisms. Since cannabinoid-induced enhancement of Acb DA is markedly attenuated by both systemic (Chen et al., 1990b; Tanda et al., 1997) and intra-VTA (Tanda et al., 1997) injections of opiate antagonists, the cannabinoid-induced enhancement of VTA–Acb DA neuronal firing and burst patterning cannot be the sole contributor to cannabinoid-enhanced Acb DA.

Another direct way to address this question is to study the effects of local cannabinoid microinjections on extracellular DA overflow in brain reward loci. This has been done (Chen et al., 1993). In those studies, THC microinfusions into the Acb dose-dependently enhanced Acb DA (Chen et al., 1993). However, while THC microinjections into the VTA dose-dependently enhanced local DA within the VTA, they did not enhance Acb DA (Chen et al., 1993). This suggests that the elevated Acb DA (and augmented brain reward functions related thereto) produced by systemic THC must result, at least in part, from local actions by THC at or near the reward-relevant Acb DA axon terminals.

Thus, in terms of sites of action, it may be hypothesized that cannabinoids enhance Acb DA by acting at various brain loci: (1) within the Acb, acting on mechanisms closely linked to axon terminal DA release; (2) within the VTA, acting on endogenous opioid mechanisms not linked to activation of neuronal firing, but rather linked to mechanisms of DA synthesis, transport, and/or release; and (3) within the VTA, acting on non-endogenous-opioid mechanisms linked to activation of neuronal firing.

6.2. *Neural mechanisms of cannabinoid action on brain reward processes*

Just as different addictive drugs enhance brain reward processes by acting at different anatomic sites within the brain's reward circuitry, different addictive drugs enhance brain reward processes by acting through different mechanisms within the brain's reward circuitry (Gardner, 1997; Wise and Gardner, 2002b). Amphetamines bind to and reverse monoamine transporters, causing presynaptic DA release (Heikkila et al., 1975a; Fischer and Cho, 1979; Nash and Brodkin, 1991; Leviel, 2001). Cocaine is a presynaptic DA reuptake blocker (Heikkila et al., 1975b). Opiates (Johnson and North, 1992) and nicotine (Grenhoff et al., 1986; Mereu et al., 1987) enhance VTA–Acb DA neuronal firing; in the case of opiates, this is transsynaptically mediated (Johnson and North, 1992) while in the case of nicotine this may be mediated by nicotinic receptors on the DA neurons themselves (Clarke and Pert, 1985). Other addictive drugs act by yet other mechanisms (Wise and Gardner, 2002b).

The question arises as to the mechanisms of cannabinoid action on brain reward processes, a question obviously related to the issues raised in

the previous section on brain sites of cannabinoid action.

As noted in the previous section, studies using local intracerebral THC microinjections lend support to the hypothesis that one of THC's sites of action is in the vicinity of the reward-relevant Acb DA axon terminals (Chen et al., 1993). As also noted above, THC-induced Acb DA augmentation is calcium-dependent and tetrodotoxin-sensitive (Chen et al., 1990b; Gardner and Lowinson, 1991; Gardner, 1992), implicating an action-potential-dependent mechanism. Additional studies, using in vivo voltammetric electrochemistry to measure THC-induced extracellular DA overflow in forebrain DA terminal loci, show 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). Additional studies support this hypothesis. First, studies of the effects of various combinations of THC and the DA antagonist haloperidol on Acb DA using in vivo brain microdialysis have been carried out (Gardner et al., 1990b). The rationale for this 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 has 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 synergistic effect on DA is a highly characteristic neuropharmacological 'signature' of co-administration of a DA antagonist such as haloperidol and a DA reuptake blocker such as GBR-12909 (Shore et al., 1979; Westerink et al., 1987). This suggests that the synergistic enhancement of haloperidol-induced augmentation of Acb DA by THC may result from THC acting as a DA reuptake blocker (possibly indirectly or transsynaptically) at Acb DA terminals (Gardner et al., 1990b; Gardner and Lowinson, 1991; Gardner, 1992). This hypothesis has also been explored using in vivo microdialysis measurements of the DA metabolite 3-methoxytyramine (3-MT; Chen et al., 1994). While only a small portion of released DA is metabolized to it, 3-MT is believed to be a sensitive index of enhanced extracellular DA (Wood and Altar, 1988) and, most importantly, a sensitive marker for distinguishing DA releasing agents from DA reuptake blockers (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). Studies were therefore undertaken on the effects of amphetamine, cocaine, nomifensine, and THC on extracellular Acb 3-MT levels using in vivo microdialysis. The DA releaser amphetamine significantly increased both DA and 3-MT in Acb, while the DA reuptake blockers cocaine and nomifensine increased only DA (Chen et al., 1994). 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 previously noted (Banerjee et al., 1975; Poddar and Dewey, 1980; Hershkowitz and Szechtman, 1979). We have hypothesized that such a mechanism may underlie cannabinoid action on DA reward processes locally within the Acb (Chen et al., 1994). Cannabinoid action within the VTA—acting on endogenous opioid mechanisms not linked to activation of neuronal firing, but rather linked to mechanisms of DA synthesis, transport, and/or release—may be mediated by a cannabinoid-receptor inhibition of an inhibitory endogenous opioid peptidergic synaptic link to VTA DA neurons that regulates their synthesis, transport, and/or release of DA rather than cell firing. Cannabinoid action within the VTA acting—on non-endogenous-opioid mechanisms linked to activation of neuronal firing—could conceivably be mediated by a cannabinoid-receptor inhibition of feedback Acb–VTA projection neurons which normally exert inhibitory synaptic tone on VTA DA cells. These conceptions are congruent with the known co-localization of cannabinoid receptors with DA D1 receptors on striatonigral inhibitory projection neurons (Herkenham et al., 1991).

7. Summary

On the basis of more than 15 years of electrophysiological and biochemical evidence, cannabinoids appear to enhance brain reward processes in similar fashion to other addictive drugs. 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. Behaviorally, cannabinoids produce CPP, are self-administered, and trigger relapse to drug-seeking behavior in the reinstatement model—all of which are hallmarks of addictive drug action. Cannabinoids are euphorigenic in humans and have addictive liability, but were long considered 'anomalous'—lacking pharmacological action on brain reward processes, on the dysphoric brain processes activated in withdrawal, or on drug-seeking and drug-taking behaviors. This position is no longer tenable. Rather, cannabinoids appear to share a common final neural action with other addictive drugs, i.e. acute activation of the VTA–Acb DA reward circuit and activation of reward-related behaviors, together with inhibition of brain reward circuitry and activation of amygdaloid CRF systems during withdrawal.

Acknowledgements

Cannabinoid research cited in this paper from the author's laboratory was supported by research grants from the US Public Health Service, National Institutes of Health (grants AA09547, DA02089, DA03622, and RR05397); the US National Science Foundation (grant BNS-86-09351); the Natural Sciences and Engineering Research Council of Canada; the New York State Office of Alcoholism and Substance Abuse Services; the New York State Office of Mental Health; the Aaron Diamond Foundation; the Julia Sullivan Medical Research Fund; and the Old Stones Foundation. The work of the following former and present students, postdoctoral fellows, and laboratory technicians is gratefully acknowledged: Thomas Seeger, Jules Nazzaro, Pierre Vaysse, Jean Max Ng Cheong Ton, Cassandra Milling, Amy Donner, David Cohen, David Morrison, Jianping Chen, Jin Li, Diane Smith, Ronen Marmur, Eric Rosenbaum, Addy Pulles, Virginia Savage, Daniel Matalon, Michael Froehler, Jordan Spector, Marino Lepore, Xinhe Liu, Robert Hayes, Stanislav Robert Vorel, William Paredes, Arlene Campos, and Jeremy Gilbert. Preparation of this manuscript was supported by the Intramural Research Program, National Institute on Drug Abuse, US Public Health Service.

References

Aceto, M.D., Scates, S.M., Lowe, J.A., Martin, B.R., 1996. Dependence on delta 9-tetrahydrocannabinol: studies on precipitated and abrupt withdrawal. J. Pharmacol. Exp. Ther. 278, 1290–1295.

Aceto, M.D., Scates, S.M., Lowe, J.A., Martin, B.R., 2001. Spontaneous and precipitated withdrawal from a synthetic cannabinoid, WIN 55,212-2. Eur. J. Pharmacol. 416, 75–81.

Amit, Z., Smith, B.R., Sutherland, E.A., 1987. Oral self-administration of alcohol: a valid approach to the study of drug self-administration and human alcoholism. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 161–171.

Anthony, J.C., Warner, L.A., Kessler, R.C., 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from National Comorbidity Study. Exp. Clin. Psychopharmacol. 2, 244–268.

Banerjee, S.P., Snyder, S.H., Mechoulam, R., 1975. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J. Pharmacol. Exp. Ther. 194, 74–81.

Bardo, M.T., 1998. Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. Crit. Rev. Neurobiol. 12, 37–67.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience. Brain Res. Rev. 28, 309–369.

Bindra, D., 1968. Neuropsychological interpretation of the effects of drive and incentive-motivation on general activity and instrumental behavior. Psychol. Rev. 75, 1–22.

Bloom, A.S., 1982. The effect of Δ^9-tetrahydrocannabinol on the synthesis of dopamine and norepinephrine in mouse brain synaptosomes. J. Pharmacol. Exp. Ther. 221, 97–103.

Bloom, A.S., Dewey, W.L., 1978. A comparison of some pharmacological actions of morphine and Δ^9-tetrahydrocannabinol in the mouse. Psychopharmacology 57, 243–248.

Bloom, A.S., Dewey, W.L., Harris, L.S., Brosius, K.K., 1977. 9-Nor-9beta-hydroxyhexahydrocannabinol, a cannabinoid

with potent antinociceptive activity: comparisons with morphine. J. Pharmacol. Exp. Ther. 200, 263–270.
Blum, K., Cull, J.G., Braverman, E.R., Comings, D.E., 1996a. Reward deficiency syndrome. Am. Scientist 84, 132–145.
Blum, K., Sheridan, P.J., Wood, R.C., Braverman, E.R., Chen, T.J., Cull, J.G., Comings, D.E., 1996b. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J. R. Soc. Med. 89, 396–400.
Bozarth, M.A., Wise, R.A., 1984. Anatomically distinct opiate receptor fields mediate reward and physical dependence. Science 244, 516–517.
Brady, J.V., Lucas, S.E., 1984. Testing Drugs for Physical Dependence Potential and Abuse Liability (NIDA Res. Monogr. 52). US Government Printing Office, Washington, DC.
Brady, J.V., Griffiths, R.R., Hienz, R.D., Ator, N.A., Lukas, S.E., Lamb, R.J., 1987. Assessing drugs for abuse liability and dependence potential in laboratory primates. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 45–85.
Braida, D., Pozzi, M., Cavallini, R., Sala, M., 2001a. Conditioned place preference induced by the cannabinoid agonist CP 55,940: interaction with the opioid system. Neuroscience 104, 923–926.
Braida, D., Pozzi, M., Parolaro, D., Sala, M., 2001b. Intracerebral self-administration of the cannabinoid receptor agonist CP 55,940 in the rat: interaction with the opioid system. Eur. J. Pharmacol. 413, 227–234.
Cadogan, A.K., Alexander, S.P., Boyd, E.A., Kendall, D.A., 1997. Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. J. Neurochem. 69, 1131–1137.
Cador, M., Robbins, T.W., Everitt, B.J., 1989. Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. Neuroscience 30, 77–86.
Cannon, D.S., Carrell, L.E., 1987. Rat strain differences in ethanol self-administration and taste aversion. Pharmacol. Biochem. Behav. 28, 57–63.
Carlezon, W.A., Jr, Wise, R.A., 1996. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. J. Neurosci. 16, 3112–3122.
Carney, J.M., Uwaydah, I.M., Balster, R.L., 1977. Evaluation of a suspension system for intravenous self-administration of water insoluble substances in the rhesus monkey. Pharmacol. Biochem. Behav. 7, 357–364.
Castañeda, E., Moss, D.E., Oddie, S.D., Whishaw, I.Q., 1991. THC does not affect striatal dopamine release: microdialysis in freely moving rats. Pharmacol. Biochem. Behav. 40, 587–591.
Chaperon, F., Soubrie, P., Puech, A.J., Thiebot, M.H., 1998. Involvement of central cannabinoid (CB_1) receptors in the establishment of place conditioning in rats. Psychopharmacology 135, 324–332.
Cheer, J.F., Kendall, D.A., Marsden, C.A., 2000. Cannabinoid receptors and reward in the rat: a conditioned place preference study. Psychopharmacology 151, 25–30.
Chen, J., Paredes, W., Li, J., Smith, D., Gardner, E.L., 1989. In vivo brain microdialysis studies of Δ^9-tetrahydrocannabinol on presynaptic dopamine efflux in nucleus accumbens of the Lewis rat. Soc. Neurosci. Abstr. 15, 1096.
Chen, J., Paredes, W., Lowinson, J.H., Gardner, E.L., 1990a. Δ^9-Tetrahydrocannabinol enhances presynaptic dopamine efflux in medial prefrontal cortex. Eur. J. Pharmacol. 190, 259–262.
Chen, J., Paredes, W., Li, J., Smith, D., Lowinson, J., Gardner, E.L., 1990b. 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 102, 156–162.
Chen, J., Paredes, W., Lowinson, J.H., Gardner, E.L., 1991. Strain-specific facilitation of dopamine efflux by Δ^9-tetrahydrocannabinol in the nucleus accumbens of rat: an *in vivo* microdialysis study. Neurosci. Lett. 129, 136–140.
Chen, J., Marmur, R., Pulles, A., Paredes, W., Gardner, E.L., 1993. 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. 621, 65–70.
Chen, J., Paredes, W., Gardner, E.L., 1994. 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. 141, 312.
Childers, S.R., Fleming, L., Konkoy, C., Marckel, D., Pacheco, M., Sexton, T., Ward, S., 1992. Opioid and cannabinoid receptor inhibition of adenylyl cyclase in brain. Ann. New York Acad. Sci. 654, 33–51.
Clarke, P.B.S., Pert, A., 1985. Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Res. 348, 355–358.
Cook, S.A., Lowe, J.A., Martin, B.R., 1998. CB1 receptor antagonist precipitates withdrawal in mice exposed to Δ^9-tetrahydrocannabinol. J. Pharmacol. Exp. Ther. 285, 1150–1156.
Corcoran, M.E., Amit, Z., 1974. Reluctance of rats to drink hashish suspensions: free-choice and forced consumption, and the effects of hypothalamic stimulation. Psychopharmacologia 35, 129–147.
Crowley, T.J., Macdonald, M.J., Whitmore, E.A., Mikulich, S.K., 1998. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. Drug Alcohol Depend. 50, 27–37.
Deneau, G.A., Kaymakçalan, S., 1971. Physiological and psychological dependence to synthetic Δ^9-tetrahydrocannabinol (THC) in rhesus monkeys. Pharmacologist 13, 246.
De Vries, T.J., Shaham, Y., Homberg, J.R., Crombag, H., Schuurman, K., Dieben, J., Vanderschuren, L.J.M.J., Schoffelmeer, A.N.M., 2001. A cannabinoid mechanism in relapse to cocaine seeking. Nat. Med. 7, 1151–1154.

de Wit, H., Stewart, J., 1981. Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology 75, 134–143.

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

Diana, M., Melis, M., Gessa, G.L., 1998a. Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur. J. Neurosci. 10, 2825–2830.

Diana, M., Melis, M., Muntoni, A.L., Gessa, G.L., 1998b. Mesolimbic dopaminergic decline after cannabinoid withdrawal. Proc. Natl. Acad. Sci. USA 95, 10269–10273.

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

Di Chiara, G., Imperato, A., 1986. Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with transcerebral dialysis in freely moving rats. Ann. New York Acad. Sci. 473, 367–381.

Erb, S., Shaham, Y., Stewart, J., 1996. Stress reinstates cocaine-seeking behavior after prolonged extinction and drug-free periods. Psychopharmacology 128, 408–412.

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

Everitt, B.J., Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P., Robbins, T.W., 1999. Associative processes in addiction and reward: the role of amygdala-ventral striatal subsystems. Ann. New York Acad. Sci. 877, 412–438.

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

Fischer, J.F., Cho, A.K., 1979. Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model. J. Pharmacol. Exp. Ther. 208, 203–209.

Frank, R.A., Martz, S., Pommering, T., 1988. The effect of chronic cocaine on self-stimulation train-duration thresholds. Pharmacol. Biochem. Behav. 29, 755–758.

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

French, E.D., 1997. Δ^9-Tetrahydrocannabinol excites rat VTA dopamine neurons through activation of cannabinoid CB1 but not opioid receptors. Neurosci. Lett. 226, 159–162.

French, E.D., Dillon, K., Wu, X., 1997. Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. Neuroreport 8, 649–652.

Fudala, P.J., Iwamoto, E.T., 1990. Conditioned aversion after delay place conditioning with amphetamine. Pharmacol. Biochem. Behav. 35, 89–92.

Fudala, P.J., Teoh, K.W., Iwamoto, E.T., 1985. Pharmacologic characterization of nicotine-induced conditioned place preference. Pharmacol. Biochem. Behav. 22, 237–241.

Gaffan, D., 1992. Amygdala and the memory of reward. In: Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion. Wiley, New York, pp. 471–483.

Gallistel, C.R., Shizgal, P., Yeomans, J.S., 1981. A portrait of the substrate for self-stimulation. Psychol. Rev. 88, 228–273.

Gardner, E.L., 1992. Cannabinoid interaction with brain reward systems—the neurobiological basis of cannabinoid abuse. In: Murphy, L.L., Bartke, A. (Eds.), Marijuana/Cannabinoids: Neurobiology and Neurophysiology. CRC Press, New York, pp. 275–335.

Gardner, E.L., 1997. Brain reward mechanisms. In: Lowinson, J.H., Ruiz, P., Millman, R.B., Langrod, J.G. (Eds.), Substance Abuse: A Comprehensive Textbook, third ed. Williams & Wilkins, Baltimore, pp. 51–85.

Gardner, E.L., 1999. The neurobiology and genetics of addiction: implications of the 'reward deficiency syndrome' for therapeutic strategies in chemical dependency. In: Elster, J. (Ed.), Addiction: Entries and Exits. Russell Sage, New York, pp. 57–119.

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

Gardner, E.L., Lowinson, J.H., 1991. Marijuana's interaction with brain reward systems: update 1991. Pharmacol. Biochem. Behav. 40, 571–580.

Gardner, E.L., Lowinson, J.H., 1993. Drug craving and positive/negative hedonic brain substrates activated by addicting drugs. Semin. Neurosci. 5, 359–368.

Gardner, E.L., Vorel, S.R., 1998. Cannabinoid transmission and reward-related events. Neurobiol. Dis. 5, 502–533.

Gardner, E.L., Paredes, W., Smith, D., Donner, A., Milling, C., Cohen, D., Morrison, D., 1988a. Facilitation of brain stimulation reward by Δ^9-tetrahydrocannabinol. Psychopharmacology 96, 142–144.

Gardner, E.L., Paredes, W., Smith, D., Seeger, T., Donner, A., Milling, C., Cohen, D., Morrison, D., 1988b. Strain-specific sensitization of brain stimulation reward by Δ^9-tetrahydrocannabinol in laboratory rats. Psychopharmacology 96 (suppl), 365.

Gardner, E.L., Chen, J., Paredes, W., Li, J., Smith, D., 1989a. 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. 15, 638.

Gardner, E.L., Paredes, W., Smith, D., Zukin, R.S., 1989b. Facilitation of brain stimulation reward by Δ^9-tetrahydrocannabinol is mediated by an endogenous opioid mechanism. Adv. Biosci. 75, 671–674.

Gardner, E.L., Chen, J., Paredes, W., Smith, D., Li, J., Lowinson, J., 1990a. Enhancement of presynaptic dopamine efflux in brain by Δ^9-tetrahydrocannabinol is mediated by an endogenous opioid mechanism. In: van Ree, J.M., Mulder, A.H., Wiegant, V.M., van Wimersma Greidanus, T.B. (Eds.), New Leads in Opioid Research. Elsevier, Amsterdam, pp. 243–245.

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

Gardner, E.L., Liu, X., Paredes, W., Savage, V., Lowinson, J., Lepore, M., 1995. Strain-specific differences in Δ^9-tetrahydrocannabinol (THC)-induced facilitation of electrical brain stimulation reward (BSR). Soc. Neurosci. Abstr. 21, 177.

George, F.R., 1987. Genetic and environmental factors in ethanol self-administration. Pharmacol. Biochem. Behav. 27, 379–384.

George, F.R., Goldberg, S.R., 1989. Genetic approaches to the analysis of addiction processes. Trends Pharmacol. Sci. 10, 78–83.

George, F.R., Meisch, R.A., 1984. Oral narcotic intake as a reinforcer: genotype × environment interaction. Behav. Genet. 14, 603.

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

Gessa, G.L., Melis, M., Muntoni, A.L., Diana, M., 1998. Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB_1 receptors. Eur. J. Pharmacol. 341, 39–44.

Gifford, A.N., Gardner, E.L., Ashby, C.R., Jr, 1997. The effect of intravenous administration of delta-9-tetrahydrocannabinol on the activity of A10 dopamine neurons recorded in vivo in anesthetized rats. Neuropsychobiology 36, 96–99.

Goett, J.M., Kay, E.J., 1981. Lithium chloride and delta-9-THC lead to conditioned aversions in the pigeon. Psychopharmacology 72, 215–216.

Goldberg, S.R., Munzar, P., Justinova, Z., Tanda, G.L., 2001. Effects of naltrexone on intravenous self-administration of delta-9-tetrahydrocannabinol (THC) by squirrel monkeys under fixed-ratio and second-order schedules. In: Abstracts of the 2001 Symposium on the Cannabinoids. International Cannabinoid Research Society, Burlington, VT, p. 102.

Goldstein, A., 2001. Addiction: From Biology to Drug Policy, second ed.. Oxford University Press, New York.

Goldstein, A., Kalant, H., 1990. Drug policy: striking the right balance. Science 249, 1513–1521.

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

Grenhoff, J., Aston-Jones, G., Svensson, T.H., 1986. Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol. Scand. 128, 351–358.

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

Grimm, J.W., See, R.E., 2000. Dissociation of primary and secondary reward-relevant limbic nuclei in an animal model of relapse. Neuropsychopharmacology 22, 473–479.

Guitart, X., Beitner-Johnson, D., Nestler, E.J., 1992. Fischer and Lewis rat strains differ in basal levels of neurofilament proteins and in their regulation by chronic morphine. Synapse 12, 242–253.

Gysling, K., Wang, R.Y., 1983. Morphine-induced activation of A10 dopamine neurons in the rat. Brain Res. 277, 119–127.

Hall, W., Solowij, N., Lemon, J., 1994. The Health and Psychological Consequences of Cannabis Use (National Drug Strategy Monograph Series No. 25). Australian Government Publishing Service, Canberra.

Harris, R.T., Waters, W., McLendon, D., 1974. Evaluation of reinforcing capability of Δ^9-tetrahydrocannabinol in monkeys. Psychopharmacologia 37, 23–29.

Hayes, R.J., Vorel, S.R., Spector, J., Liu, X., Gardner, E.L., 2002. Electrical and chemical stimulation of the basolateral complex of the amygdala reinstates cocaine-seeking behavior in the rat. Psychopharmacology, in press.

Heal, D.J., Frankland, A.T.J., Buckett, W.R., 1990. 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 29, 1141–1150.

Heikkila, R.E., Orlansky, H., Mytilineou, C., Cohen, G., 1975a. Amphetamine: evaluation of *d*- and *l*-isomers as releasing agents and uptake inhibitors for ^{3}H-dopamine and ^{3}H-norepinephrine in slices of rat neostriatum and cerebral cortex. J. Pharmacol. Exp. Ther. 194, 47–56.

Heikkila, R.E., Orlansky, H., Cohen, G., 1975b. Studies on the distinction between uptake inhibition and release of (^{3}H) dopamine in rat brain tissue slices. Biochem. Pharmacol. 24, 847–852.

Herkenham, M., Lynn, A.B., de Costa, B.R., Richfield, E.K., 1991. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. Brain Res. 547, 267–274.

Hershkowitz, M., Szechtman, H., 1979. Pretreatment with Δ^1-tetrahydrocannabinol and psychoactive drugs: effects on uptake of biogenic amines and on behavior. Eur. J. Pharmacol. 59, 267–276.

Hershkowitz, M., Goldman, R., Raz, A., 1977. Effect of cannabinoids on neurotransmitter uptake, ATPase activity and morphology of mouse brain synaptosomes. Biochem. Pharmacol. 26, 1327–1331.

Hiroi, N., White, N.M., 1991. The lateral nucleus of the amygdala mediates expression of the amphetamine conditioned place preference. J. Neurosci. 11, 2107–2116.

Hutcheson, D.M., Tzavara, E.T., Smadja, C., Valjent, E., Roques, B.P., Hanoune, J., Maldonado, R., 1998. Behavioural and biochemical evidence for signs of abstinence in mice chronically treated with Δ-9-tetrahydrocannabinol. Br. J. Pharmacol. 125, 1567–1577.

Jentsch, J.D., Wise, A., Katz, Z., Roth, R.H., 1998. Alpha-noradrenergic receptor modulation of the phencyclidine- and Δ^9-tetrahydrocannabinol-induced increases in dopamine utilization in rat prefrontal cortex. Synapse 28, 21–26.

Johnson, S.W., North, R.A., 1992. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci. 12, 483–488.

Johnson, K.M., Dewey, W.L., Harris, L.S., 1976. Some structural requirements for inhibition of high-affinity synaptosomal serotonin uptake by cannabinoids. Mol. Pharmacol. 12, 345–352.

Johnson, P.I., Goodman, J.B., Condon, R., Stellar, J.R., 1995. Reward shifts and motor responses following microinjections of opiate-specific agonists into either the core or shell of the nucleus accumbens. Psychopharmacology 120, 195–202.

Jorenby, D.E., Steinpreis, R.E., Sherman, J.E., Baker, T.B., 1990. Aversion instead of preference learning indicated by nicotine place conditioning in rats. Psychopharmacology 101, 533–538.

Katner, S.N., Magalong, J.G., Weiss, F., 1999. Reinstatement of alcohol-seeking behavior by drug-associated discriminative stimuli after prolonged extinction in the rat. Neuropsychopharmacology 20, 471–479.

Kaymakçalan, S., 1972. Physiology and psychological dependence on THC in rhesus monkeys. In: Paton, W.D.M., Crown, J. (Eds.), Cannabis and its Derivatives. Oxford University Press, London, pp. 142–149.

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

Khodzhagel'diev, T., 1986. 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. 101, 48–50.

Kleber, H.D., 1988. Introduction—cocaine abuse: historical, epidemiological, and psychological perspectives. J. Clin. Psychiatry 49 (2) (Suppl.) 3–6.

Koob, G.F., 1996. Drug addiction: the yin and yang of hedonic homeostasis. Neuron 16, 893–896.

Koob, G.F., 1999. The role of the striatopallidal and extended amygdala systems in drug addiction. Ann. New York Acad. Sci. 877, 445–460.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.

Koob, G.F., Markou, A., Weiss, F., Schulteis, G., 1993. Opponent process and drug dependence: neurobiological mechanisms. Semin. Neurosci. 5, 351–358.

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

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

Kosten, T.A., Miserendino, M.J., Chi, S., Nestler, E.J., 1994. 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. 269, 137–144.

Kosten, T.A., Miserendino, M.J., Haile, C.N., DeCaprio, J.L., Jatlow, P.I., Nestler, E.J., 1997. Acquisition and maintenance of intravenous cocaine self-administration in Lewis and Fischer inbred rat strains. Brain Res. 778, 418–429.

Kozel, N.J., Adams, E.H., 1986. Epidemiology of drug abuse: an overview. Science 234, 970–974.

Laszlo, J., Lucas, V.S., Hanson, D.C., Cronin, C.M., Sallan, S.E., 1981. Levonantradol for chemotherapy-induced emesis: phase I–II oral administration. J. Clin. Pharmacol. 21, 51S–56S.

Ledent, C., Valverde, O., Cossu, G., Petitet, F., Aubert, J.F., Beslot, F., Bohme, G.A., Imperato, A., Pedrazzini, T., Roques, B.P., Vassart, G., Fratta, W., Parmentier, M., 1999. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB_1 receptor knockout mice. Science 283, 401–404.

Leite, J.R., Carlini, E.A., 1974. Failure to obtain 'cannabis directed behavior' and abstinence syndrome in rats chronically treated with cannabis sativa extracts. Psychopharmacologia 36, 133–145.

Lepore, M., Vorel, S.R., Lowinson, J., Gardner, E.L., 1995. Conditioned place preference induced by Δ^9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. Life Sci. 56, 2073–2080.

Lepore, M., Liu, X., Savage, V., Matalon, D., Gardner, E.L., 1996. 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. 58, PL365–PL372.

Leviel, V., 2001. The reverse transport of DA, what physiological significance? Neurochem. Int. 38, 83–106.

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

Mallet, P.E., Beninger, R.J., 1998. Δ^9-Tetrahydrocannabinol, but not the endogenous cannabinoid receptor ligand anandamide, produces conditioned place aversion. Life Sci. 62, 2431–2439.

Malone, D.T., Taylor, D.A., 1999. Modulation by fluoxetine of striatal dopamine release following Δ^9-tetrahydrocannabinol: a microdialysis study in conscious rats. Br. J. Pharmacol. 128, 21–26.

Mansbach, R.S., Nicholson, K.L., Martin, B.R., Balster, R.L., 1994. Failure of Δ^9-tetrahydrocannabinol and CP 55,940 to maintain intravenous self-administration under a fixed-interval schedule in rhesus monkeys. Behav. Pharmacol. 5, 219–225.

Martellotta, M.C., Cossu, G., Fattore, L., Gessa, G.L., Fratta, W., 1998. Self-administration of the cannabinoid receptor agonist WIN 55,212-2 in drug-naive mice. Neuroscience 85, 327–330.

McBride, W.J., Murphy, J.M., Ikemoto, S., 1999. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav. Brain Res. 101, 129–152.

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

McGregor, I.S., Issakidis, C.N., Prior, G., 1996. Aversive effects of the synthetic cannabinoid CP 55,940 in rats. Pharmacol. Biochem. Behav. 53, 657–664.

Meil, W.M., See, R.E., 1996. Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. Behav. Pharmacol. 7, 754–763.

Meisch, R.A., Carroll, M.E., 1987. Oral drug self-administration: drugs as reinforcers. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 143–160.

Melis, M., Muntoni, A.L., Diana, M., Gessa, G.L., 1996. The cannabinoid receptor agonist WIN 55,212-2 potently stimulates dopaminergic neuronal activity in the mesolimbic system. Behav. Pharmacol. 7 (Suppl. 1), 68.

Mereu, G., Yoon, K.-W.P., Boi, V., Gessa, G.L., Naes, L., Westfall, T.C., 1987. Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. Eur. J. Pharmacol. 141, 395–400.

Merlo Pich, E., Lorang, M., Yeganeh, M., Rodríguez de Fonseca, F., Raber, J., Koob, G.F., Weiss, F., 1995. 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. 15, 5439–5447.

Misenrendino, M.J.D., Kosten, T.A., Guitart, X., Chi, S., Nestler, E.J., 1992. Individual differences in vulnerability to drug addiction: behavioral and biochemical correlates. Soc. Neurosci. Abstr. 18, 1078.

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

Napier, T.C., Mitrovic, I., 1999. Opioid modulation of ventral pallidal inputs. Ann. New York Acad. Sci. 877, 176–201.

Nash, J.F., Brodkin, J., 1991. Microdialysis studies on 3,4-methylenedioxymethamphetamine induced dopamine release: effect of dopamine uptake inhibitors. J. Pharmacol. Exp. Ther. 259, 820–825.

Navarro, M., Fernández-Ruiz, J.J., de Miguel, R., Hernández, M.L., Cebeira, M., Ramos, J.A., 1993. An acute dose of δ^9-tetrahydrocannabinol affects behavioral and neurochemical indices of mesolimbic dopaminergic activity. Behav. Brain Res. 57, 37–46.

Navarro, M., Chowen, J., Carrera, M.R.A., del Arco, I., Villanúa, M.A., Martin, Y., Roberts, A.J., Koob, G.F., Rodríguez de Fonseca, F., 1998. CB_1 cannabinoid receptor antagonist-induced opiate withdrawal in morphine-dependent rats. Neuroreport 9, 3397–3402.

Nestler, E.J., 1993. Molecular mechanisms of drug addiction in the mesolimbic dopamine pathway. Semin. Neurosci. 5, 369–376.

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

Ng Cheong Ton, J.M., Gerhardt, G.A., Friedemann, M., Etgen, A.M., Rose, G.M., Sharpless, N.S., Gardner, E.L., 1988. 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. 451, 59–68.

Noyes, J.R., Brunk, S.F., Avery, D.H., Canter, A., 1975. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin. Pharmacol. Ther. 18, 84–89.

Overton, P.G., Clark, D., 1997. Burst firing in midbrain dopaminergic neurons. Brain Res. Rev. 25, 312–334.

Parker, L.A., Gillies, T., 1995. THC-induced place and taste aversions in Lewis and Sprague–Dawley rats. Behav. Neurosci. 109, 71–78.

Parsons, L.H., Smith, A.D., Justice, J.B., Jr, 1991. Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse 9, 60–65.

Peoples, L.L., Uzwiak, A.J., Gee, F., Fabbricatore, A.T., Muccino, K.J., Mohta, B.D., West, M.O., 1999. Phasic accumbal firing may contribute to the regulation of drug taking during intravenous cocaine self-administration. Ann. New York Acad. Sci. 877, 781–787.

Pickens, R., Thompson, T., Muchow, D.C., 1973. Cannabis and phencyclidine self-administered by animals. In: Goldfarb, L., Hoffmeister, F. (Eds.), Psychic Dependence [Bayer-Symposium IV]. Springer, Berlin, pp. 78–86.

Poddar, M.K., Dewey, W.L., 1980. Effects of cannabinoids on catecholamine uptake and release in hypothalamus and striatal synaptosomes. J. Pharmacol. Exp. Ther. 214, 63–67.

Pontieri, F.E., Tanda, G., Di Chiara, G., 1995. Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the 'shell' as compared with the 'core' of the rat nucleus accumbens. Proc. Natl. Acad. Sci. USA 92, 12304–12308.

Pothos, E., Rada, P., Mark, G.P., Hoebel, B.G., 1991. Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. Brain Res. 566, 348–350.

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

Redgrave, P., Prescott, T.J., Gurney, K., 1999. Is the short-latency dopamine response too short to signal reward error? Trends Neurosci. 22, 146–151.

Richardson, N.R., Roberts, D.C.S., 1996. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J. Neurosci. Methods 66, 1–11.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Rev. 18, 247–291.

Rodríguez de Fonseca, F., Carrera, M.R.A., Navarro, M., Koob, G.F., Weiss, F., 1997. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. Science 276, 2050–2054.

Rossetti, Z.L., Hmaidan, Y., Gessa, G.L., 1992. Marked inhibition of mesolimbic dopamine release: a common

feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur. J. Pharmacol. 221, 227–234.
Rubino, T., Tizzoni, L., Viganò, D., Massi, P., Parolaro, D., 1997. Modulation of rat brain cannabinoid receptors after chronic morphine treatment. Neuroreport 8, 3219–3223.
Sañudo-Peña, M.C., Tsou, K., Delay, E.R., Hohman, A.G., Force, M., Walker, J.M., 1997. Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. Neurosci. Lett. 223, 125–128.
Schaefer, G.J., Michael, R.P., 1986. Changes in response rates and reinforcement thresholds for intracranial self-stimulation during morphine withdrawal. Pharmacol. Biochem. Behav. 25, 1263–1269.
Schechter, M.D., Calcagnetti, D.J., 1993. Trends in place preference conditioning with a cross-indexed bibliography; 1957–1991. Neurosci. Biobehav. Rev. 17, 21–41.
Schulteis, G., Markou, A., Gold, L.H., Stinus, L., Koob, G.F., 1994. Relative sensitivity of multiple indices of opiate withdrawal: a quantitative dose–response analysis. J. Pharmacol. Exp. Ther. 271, 1391–1398.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.
Self, D.W., Nestler, E.J., 1995. Molecular mechanisms of drug reinforcement and addiction. Annu. Rev. Neurosci. 18, 463–495.
Shaham, Y., Stewart, J., 1995. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology 119, 334–341.
Shaham, Y., Rajabi, H., Stewart, J., 1996. Relapse to heroin-seeking in rats under opioid maintenance: the effects of stress, heroin-priming, and withdrawal. J. Neurosci. 16, 1957–1963.
Shalev, U., Grimm, J.W., Shaham, Y., 2002. Neurobiology of relapse to heroin and cocaine seeking: a review. Pharmacol. Rev. 54, 1–42.
Shizgal, P., 1997. Neural basis of utility estimation. Curr. Opin. Neurobiol. 7, 198–208.
Shore, P.A., McMillen, B.A., Miller, H.H., Sanghera, M.K., Kiserand, R.S., German, D.C., 1979. The dopamine neuronal storage system and non-amphetamine psychotogenic stimulants: a model for psychosis. In: Usdin, E., Kopin, I.J., Barchas, J. (Eds.), Catecholamines: Basic and Clinical Frontiers. Pergamon Press, New York, pp. 722–735.
Simon, D., Burns, E., 1997. The Corner: A Year in the Life of an Inner-City Neighborhood. Broadway Books (Random House), New York.
Stewart, J., 1984. Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. Pharmacol. Biochem. Behav. 20, 917–923.
Stewart, J., de Wit, H., 1987. Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 211–227.
Stewart, J., Vezina, P., 1988. A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. Brain Res. 457, 287–294.
Suzuki, T., George, F.R., Meisch, R.A., 1989. Differential establishment and maintenance of oral ethanol reinforced behavior in Lewis and Fischer 344 inbred rat strains. J. Pharmacol. Exp. Ther. 245, 164–170.
Szabo, B., Muller, T., Koch, H., 1999. Effects of cannabinoids on dopamine release in the corpus striatum and the nucleus accumbens in vitro. J. Neurochem. 73, 1084–1089.
Takahashi, R.N., Singer, G., 1979. Self-administration of Δ^9-tetrahydrocannabinol by rats. Pharmacol. Biochem. Behav. 11, 737–740.
Takahashi, R.N., Singer, G., 1980. Effects of body weight levels on cannabis self-administration. Pharmacol. Biochem. Behav. 13, 877–881.
Takahashi, R.N., Singer, G., 1981. Cross self-administration of delta 9-tetrahydrocannabinol and D-amphetamine in rats. Braz. J. Med. Biol. Res. 14, 395–400.
Tanda, G., Pontieri, F.E., Di Chiara, G., 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. Science 276, 2048–2050.
Tanda, G., Loddo, P., Di Chiara, G., 1999. Dependence of mesolimbic dopamine transmission on Δ^9-tetrahydrocannabinol. Eur. J. Pharmacol. 376, 23–26.
Tanda, G., Munzar, P., Goldberg, S.R., 2000. Self-administration behavior is maintained by the psychoactive ingredient in marijuana in squirrel monkeys. Nat. Neurosci. 3, 1073–1074.
Taylor, D.A., Sitaram, B.R., Elliot-Baker, S., 1988. Effect of Δ-9-tetrahydrocannabinol on release of dopamine in the corpus striatum of the rat. In: Chesher, G., Consroe, P., Musty, R. (Eds.), Marijuana: An International Research Report. Australian Government Publishing Service, Canberra, pp. 405–408.
Thanos, P.K., Volkow, N.D., Freimuth, P., Umegaki, H., Ikari, H., Roth, G., Ingram, D.K., Hitzemann, R., 2001. Overexpression of dopamine D2 receptors reduces alcohol self-administration. J. Neurochem. 78, 1094–1103.
Thorat, S.N., Bhargava, H.N., 1994. Evidence for a bidirectional cross-tolerance between morphine and Δ^9-tetrahydrocannabinol in mice. Eur. J. Pharmacol. 260, 5–13.
Tsou, K., Patrick, S.L., Walker, J.M., 1995. Physical withdrawal in rats tolerant to delta 9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. Eur. J. Pharmacol. 280, R13–R15.
Tzavara, E.T., Valjent, E., Firmo, C., Mas, M., Beslot, F., Defer, N., Roques, B.P., Hanoune, J., Maldonado, R., 2000. Cannabinoid withdrawal is dependent upon PKA activation in the cerebellum. Eur. J. Neurosci. 12, 1038–1046.
Tzschentke, T.M., 1998. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog. Neurobiol. 56, 613–672.
Uhl, G., Blum, K., Noble, E., Smith, S., 1993. Substance abuse vulnerability and D2 receptor genes. Trends Neurosci. 16, 83–88.

Valjent, E., Maldonado, R., 2000. A behavioural model to reveal place preference to Δ^9-tetrahydrocannabinol in mice. Psychopharmacology 147, 436–438.

van der Kooy, D., 1987. Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 229–240.

Vaysse, P.J.-J., Gardner, E.L., Zukin, R.S., 1987. Modulation of rat brain opioid receptors by cannabinoids. J. Pharmacol. Exp. Ther. 241, 534–539.

Volkow, N.D., Wang, G.-J., Fowler, J.S., Logan, J., Hitzemann, R.J., Ding, Y.-S., Pappas, N., Shea, C., Piscani, K., 1996. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcohol Clin. Exp. Res. 20, 1594–1598.

Volkow, N.D., Wang, G.-J., Fowler, J.S., Logan, J., Gatley, S.J., Hitzemann, R.J., Chen, A.D., Pappas, N., 1997. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 386, 830–833.

Volkow, N.D., Wang, G.-J., Fowler, J.S., Logan, J., Gatley, S.J., Gifford, A., Hitzemann, R.J., Ding, Y.-S., Pappas, N., 1999. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D_2 receptor levels. Am. J. Psychiatry 156, 1440–1443.

Volkow, N.D., Chang, L., Wang, G.-J., Fowler, J.S., Ding, Y.-S., Sedler, M., Logan, J., Franceschi, D., Gatley, S.J., Hitzemann, R.J., Gifford, A., Wong, C., Pappas, N., 2001. Low level of brain dopamine D_2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am. J. Psychiatry 158, 2015–2021.

Vorel, S.R., Liu, X., Hayes, R.J., Spector, J.A., Gardner, E.L., 2001. Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science 292, 1175–1178.

Weeks, J.R., Collins, R.J., 1987. Screening for drug reinforcement using intravenous self-administration in the rat. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 35–43.

Westerink, B.H., Tuntler, J., Damsma, G., Rollema, H., de Vries, J.B., 1987. The use of tetrodotoxin for the characterization of drug-enhanced dopamine release in conscious rats studied by brain dialysis. Naunyn Schmiedeberg's Arch. Pharmacol. 336, 502–507.

White, N.M., Hiroi, N., 1993. Amphetamine conditioned cue preference and the neurobiology of drug-seeking. Semin. Neurosci. 5, 329–336.

Wickelgren, I., 1997. Getting the brain's attention. Science 278, 35–37.

Wise, R.A., 1996. Addictive drugs and brain stimulation reward. Annu. Rev. Neurosci. 19, 319–340.

Wise, R.A., Bozarth, M.A., 1984. Brain reward circuitry: four circuit elements 'wired' in apparent series. Brain Res. Bull. 12, 203–208.

Wise, R.A., Gardner, E.L., 2002a. Animal models of addiction. In: Charney, D.S., Nestler, E.J., Bunney, B.S. (Eds.), Neurobiology of Mental Illness, second ed., Oxford University Press, London, in press.

Wise, R.A., Gardner, E.L., 2002b. Functional anatomy of substance-related disorders. In: D'haenen, H., den Boer, J.A., Willner, P. (Eds.), Biological Psychiatry. Wiley, New York, pp. 509–522.

Wise, R.A., Munn, E., 1995. Withdrawal from chronic amphetamine elevates baseline intracranial self-stimulation thresholds. Psychopharmacology 117, 130–136.

Wise, R.A., Murray, A., Bozarth, M.A., 1990. Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. Psychopharmacology 100, 355–360.

Wood, P.L., Altar, C.A., 1988. Dopamine release in vivo from nigrostriatal, mesolimbic, and mesocortical neurons: utility of 3-methoxytyramine measurements. Pharmacol. Rev. 40, 163–187.

Woodward, D.J., Chang, J.Y., Janak, P., Azarov, A., Anstrom, K., 1999. Mesolimbic neuronal activity across behavioral states. Ann. New York Acad. Sci. 877, 91–112.

Yanagita, T., 1987. Prediction of drug abuse liability from animal studies. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 189–198.

Yokel, R.A., 1987. Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preferences. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer, New York, pp. 1–33.