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Preclinical studies on the reinforcing effects of cannabinoids. A tribute to the scientific research of Dr. Steve Goldberg

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Abstract

Rationale—The reinforcing effects of most abused drugs have been consistently demonstrated and studied in animal models, although those of marijuana were not, until the demonstration fifteen years ago that THC could serve as a reinforcer in self-administration (SA) procedures in squirrel monkeys. Until then, those effects were inferred using indirect assessments.

Objectives—The aim of this manuscript is to review the primary preclinical procedures used to indirectly and directly infer reinforcing effects of cannabinoid drugs.

Methods—Results will be reviewed from studies of cannabinoid-discrimination, intracranial-self-stimulation (ICSS), conditioned place preference (CPP), as well as change in levels of dopamine assessed in brain areas related to reinforcement, and finally from self-administration procedures. For each procedure, an evaluation will be made of the predictive validity in detecting the potential abuse liability of cannabinoids based on seminal papers, with the addition of selected reports from more recent years especially those from Dr. Goldberg's research group.

Results and Conclusions—ICSS and CPP do not provide consistent results for the assessment of potential for abuse of cannabinoids. However, drug-discrimination and neurochemistry procedures appear to detect potential for abuse of cannabinoids, as well as several novel "designer cannabinoid drugs." Though after 15 years it remains somewhat problematic transfer the self-administration model of marijuana abuse from squirrel monkeys to other species, studies with the former species have substantially advanced the field, and several reports have been published with consistent self-administration of cannabinoid agonists in rodents.

Keywords

Cannabis; Delta-9-THC; Dopamine neurochemistry; Marijuana Substance use disorders; addiction; self-administration; drug discrimination; place conditioning; spice; Designer drugs

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Introduction

The plant cannabis, along with its “therapeutic” and psychotropic properties, was described in several ancient books. However, in contrast to the psychoactive ingredients in other plants, such as cocaine from erythroxylum coca or morphine from papaver somniferum, delta-9-tetrahydrocannabinol (THC) from cannabis, was only discovered recently (Gaoni and Mechoulam 1964). The discovery of the chemical structure of THC has greatly accelerated cannabinoid research. Indeed, until the late 1980s the observable effects of THC administration were thought to be the result of a cellular/neuronal interaction not mediated by receptors, but rather through the high lipophilicity of the THC molecule, rendering it effective in modifying the lipid structure of the cells’ membranes (Leuschner et al. 1984). CB1 receptors were identified in 1989 (Devane et al. 1988), and cloned in the early 1990s (Matsuda et al. 1990). Surprisingly, CB1 receptors are the most abundant receptors in the mammalian brains, and researchers have discovered not only one, but several endogenous circulating ligands for these receptors (Devane et al. 1992; Di Marzo and De Petrocellis 2012). However, a reliable animal model of THC self-administration was only established at the start of the new millennium. Behavioral pharmacologists struggled for about 30 years (1970–2000) to understand why the self-administration procedure was able to capture the reinforcing effects of most drugs of abuse but not of the psychoactive principle ingredient of marijuana (Tanda and Goldberg 2003), one of the most abused drugs world-wide. Inability to demonstrate THC self-administration in animal models was used to support claims for legalization of recreational use of marijuana.

In addition to the establishment of a model of reinforcing effects of THC, the last 15 years has seen a transformation of knowledge about THC in terms of physiology, pharmacology and therapeutics, and several reviews are available to cover all of these topics (De Petrocellis and Di Marzo 2010; Di Marzo 2009; Di Marzo and De Petrocellis 2012; Elkashef et al. 2008; Micale et al. 2013; Pertwee 2008; Petrosino and Di Marzo 2010; Piomelli 2003; Tanda and Goldberg 2003; Toth et al. 2009; Vandrey and Haney 2009; Vemuri and Makriyannis 2015). The present paper is not intended to be a comprehensive review of the scientific literature on cannabinoids, but instead, to serve as a review of results from the primary behavioral procedures employed to indirectly infer reinforcing effects of THC before they were directly demonstrated in squirrel monkeys (Tanda et al. 2000). Indeed, while we had scientific clinical reports on subjective effects of cannabis derivatives and their potential for abuse in humans (Block et al. 1998; Chait and Zacny 1992; Fant et al. 1998), the lack of preclinical models of reinforcing effects of THC brought several other indirect procedures to the forefront of the research about abuse liability of cannabis derivatives (Balster and Prescott 1992; Gardner and Vorel 1998).

Subjective effects of cannabinoid agonists

Administration of drugs of abuse can produce specific subjective effects that human and animal subjects can be trained to discriminate. In a typical drug-discrimination procedure, animals are trained to emit one response after administration of drug, and another response after administration of vehicle. Appropriate responses, typically pressing different levers, are

intermittently reinforced with food presentation. Thus, the subjective effect of the drug (or its absence) is the stimulus that controls on which lever presses produce food reinforcement.

As has been reported for other abused substances (Kamien et al. 1993; Schuster and Johanson 1988), both animals and human subjects can discriminate THC from vehicle (Chait et al. 1988; Wiley et al. 1993), and such effects likely play a role in the abuse liability of marijuana and other cannabis derivatives (Balster and Prescott 1992; Wiley 1999). Thus, drugs that produce in animals subjective effects similar to those produced by THC potentially induce similar subjective effects in human subjects.

The initial studies on THC drug discrimination established the relevance and specificity of the THC stimulus. Several studies tested whether natural components of marijuana smoke would substitute for THC similarly to those components when synthesized (See Table 1, Natural and Synthetic Cannabinoids)(Browne and Weissman 1981; Hiltunen and Jarbe 1986a; b; Jarbe and Henriksson 1974; Jarbe et al. 1977), and other studies aimed to test stereo-isomeric requirements as well (Browne and Weissman 1981; Jarbe et al. 1986; Jarbe et al. 1993; Jarbe et al. 1989; Jarbe et al. 1994; Mechoulam et al. 1987). It was also reported that the discriminative effects of CB1 agonists were centrally mediated (Perio et al., (1996).

Recent experiments from Dr. Goldberg's laboratory (Solinas et al. 2004) showed that, although morphine did not substitute for the discriminative stimulus effects of THC, it potentiated those effects. Indeed, β-endorphins and opioid agonists such as morphine, locally injected in the ventral tegmental area (VTA), or given systemically, potentiated the discriminative effects of small inactive doses of THC, an effect blocked by naloxone. Further, THC administration increased the concentration of endogenous opioid peptides in the VTA (see Figure 1)(Solinas et al. 2004). This effect is in agreement with both modulation of the subjective effects of THC by intra-VTA injections of β-endorphins (Solinas et al. 2004), and modulation of THC-induced increase in accumbens shell DA (Tanda et al. 1997), which was blocked by local intra-VTA μ-opioid antagonists or by systemic naloxone (Tanda et al. 1997). Although these experiments indicated that subjective effects of THC were centrally mediated, and that the opioid system is involved centrally in the behavioral effects of cannabinoids, contrasting results have been reported in human subjects (Haney 2007; Haney et al. 2003) and in non-human primates (Gerak et al. 2015; Justinova et al. 2004; Li et al. 2008; Maguire et al. 2013).

The pharmacologic specificity of the discriminative stimulus effects of THC was documented by the large number of classes of compounds that have failed to substitute for THC in drug discrimination procedures in a variety of animal species (Table 1, Non-Cannabinoid Drugs of Abuse). Full substitution for THC has been demonstrated only with drugs that are agonists at CB1 receptors (Balster and Prescott 1992; Jarbe and Henriksson 1974; Wiley et al. 1995b). However, limited substitution with some cannabinoid CB1 agonists, such as anandamide, or methanadamide has been reported. These results may be due to partial agonist effects exerted by THC, or by differences in degrees of intrinsic cannabinoid activity among different drugs (De Vry and Jentzsch 2003; Jarbe et al. 1998). Alternatively, doses that significantly decrease response rates with these compounds may be lower than those necessary for full efficacy/generalization. Intrinsic efficacy and degree of

tolerance to repeated treatment with THC have been studied and reported (Hruba et al. 2012). In that report, repeated THC injections produced extensive tolerance to its own discriminative effects. Such tolerance, however, only slightly affected the subjective effects produced by designer cannabinoid drugs with higher efficacy than THC. On the other hand, some cannabinoid CB1 agonists might have pharmacologic affinity and also bind to cannabinoid CB2, vanilloid TRPV1, GPR55, PPAR-alpha or PPAR-gamma receptors (Baskfield et al. 2004; McMahon et al. 2008). Functional activation of these receptors has been reported (Le Foll et al. 2013; Mascia et al. 2011; Mazzola et al. 2009), which may mask or interfere with the discriminative-stimulus effects mediated by CB1 receptors.

High metabolic rates may also be among the reasons for the failure of anandamide to fully substitute for THC in some tests (Solinas et al. 2007b; Stewart and McMahon 2011). Further, methanandamide, a metabolic stable analog of anandamide, does not always fully substitute for THC in standard conditions. However, it does fully substitute under appropriate conditions, in which, for example lower doses of THC are employed to train the subjects, or (to increase selectivity) the THC stimulus is being discriminated from a different drug (morphine or PCP) rather than its vehicle (Alici and Appel 2004; Burkey and Nation 1997; Jarbe et al. 1998). Further, when FAAH (fatty-acid-amide-hydrolase), the enzyme that contributes to anandamide degradation is blocked, full generalization of intravenous anandamide to the discriminative effect of THC has been reported (Solinas et al. 2007b; Stewart and McMahon 2011). It has also been recently shown that simultaneous blockade of the enzymes FAAH and MGL (which blocks 2-AG metabolism) can produce THC-like subjective effects (Hruba et al. 2015). These latter results suggest that both endocannabinoid ligand levels have to be increased in the brain to obtain generalization with the THC stimulus. Indeed, selectively blocking each enzyme alone does not produce significant THC-like subjective effects (Hruba et al. 2015).

In summary, studies of THC as a discriminative stimulus have indicated that its effects are shared only by drugs from the cannabinoid pharmacologic class (Balster and Prescott 1992; Browne and Weissman 1981; Wiley 1999) and that THC and other CB1 agonists do not substitute for other drugs of abuse when the latter are used as training drugs (Doty et al. 1994; Jarbe 1982; Li et al. 2008; Maguire et al. 2013). Further, THC discrimination studies established the central mediation and stereospecificity of the subjective effects. Though this procedure does not directly assess the abuse liability of cannabinoids, it has been an important indicator of cannabinoid specific pharmacology, and can reasonably be used to predict whether new compounds have subjective effects like those of THC. Thus THC drug-discrimination procedures might have predictive validity about abuse liability of, for example, novel cannabinoid drugs. In this respect, it is interesting to note that new cannabinoids currently abused in both USA and Europe and available online, have been reported to fully substitute for the THC discriminative stimulus (Gatch and Forster 2014; Jarbe et al. 2010) (see table 1). Further the procedure identified antagonist effects of rimonabant, which has turned out to have inverse agonist effects (Landsman et al. 1997) and important psychiatric side effects in humans (E.M.A. 2008). However this procedure shows promise for identifying pure antagonists that can effectively block the subjective effects of THC, and possibly its abuse.

Intra-cranial Self-stimulation

The discovery by Olds and Milner (1954) that electrical stimulation of particular brain sites, intra-cranial self-stimulation (ICSS), could produce reinforcing effects in rats opened up new avenues in the field of psychopharmacology. For the present purposes, the potential of abused drugs to enhance the effects of brain stimulation suggested that the abuse liability of different drugs could be tested using this procedure (Kornetsky 1985; Kornetsky and Esposito 1979; Kornetsky et al. 1979). It is worth noting that drugs of abuse from different pharmacological classes produce a similar facilitation of ICSS whereas drugs lacking abuse liability do not (Olds and Fobes 1981; Wise 1996).

The direct behavioral effects of cannabinoids under this procedure were first studied by Stark and Dews (1980). In that report, THC, nabilone and canbisol decreased response rates of rats under ICSS procedures. However, only one, and a very high, comparison dose of THC was tested (10 mg/kg). Moreover, even with a 50 percent decrease in behavior, the effect of THC was not significant due to the high variability in the control response rates. Thus, Gardner and colleagues (Gardner et al. 1989; Gardner et al. 1988) were the first to show that i.p. administration of THC (1.5 mg/kg i.p.) in male Lewis rats lowered the brain stimulation threshold. Further, the facilitation of brain stimulation was antagonized by naloxone pretreatment, suggesting the involvement of opioid mechanisms in the behavioral effects of THC on brain stimulation (Gardner et al. 1989). The authors pointed out that their results strongly suggest that THC shares with other abused drugs the ability to facilitate reward mechanism/s under the ICSS procedure. Further, THC, like other drugs, might produce its euphorigenic effects through these brain mechanisms. The positive, “drug-abuse-like” results obtained with THC in this procedure have been replicated by the same and other research groups (Katsidoni et al. 2013; Lepore et al. 1996). Nonetheless, contrasting results have often been reported, even from the same authors. For example, a lack of effect of THC and other cannabinoid agonists has been reported (Arnold et al. 2001a; Gallo et al. 2014; Vlachou et al. 2003), as well as *decreases* in the effectiveness of brain stimulation (Fokos and Panagis 2010; Katsidoni et al. 2013; Mavrikaki et al. 2010; Vlachou et al. 2005; 2006; Vlachou et al. 2007; Wiebelhaus et al. 2015), an effect that was shown to be reversed by administration of very low doses, in the μg/kg range, of CB1 receptor antagonists (Vlachou et al. 2003; 2005; Vlachou et al. 2007).

Several factors might be taken into consideration to explain the different outcomes obtained with cannabinoids under this procedure. One of these is the strain of the rats used, as Lewis, but not Sprague-Dawley or Fisher rats showed a significant leftward shift of the number of brain stimulations obtained as a function of the current frequency (the rate-frequency curve)., obtained under an ICSS procedure (Lepore et al. 1996). However, even though genetic factors may be involved in the sensitivity to cannabinoid effects and to vulnerability to THC use and dependence (Arnold et al. 2001b; Cadoni et al. 2015; Gillespie et al. 2009; Kendler et al. 2008; Martin et al. 1999; Parker and Gillies 1995), only one dose of THC was tested in the report by Lepore et al (1996), thus there is lack of information about how different specific doses of THC might influence the rate-frequency curve. Indeed, a recent report explored again the contrasting results of cannabinoids in ICSS procedures, providing more emphasis on the range of THC doses employed (Katsidoni et al. 2013). Biphasic

effects of THC on ICSS were found, with a low (0.1 mg/kg) dose decreasing and a moderate dose (1.0 mg/kg) increasing the ICSS threshold in Sprague Dawley rats. Both of these effects were blocked by rimonabant pretreatments (Katsidoni et al. 2013), confirming CB1 receptor involvement in the biphasic action of THC.

Taken together, the results obtained with cannabinoids in the ICSS procedure are widely mixed, and do not provide a level of confidence near that obtained with other drug classes to state that cannabinoid agonists would consistently produce a facilitation of brain stimulation. Thus, this methodology seems to be inadequate to understand the potential for abuse of cannabinoids or to screen either cannabinoid agonists or antagonists.

Place Conditioning

In place conditioning studies, subjects are confined inside one of the two distinguishable compartments during the conditioning session(s) with the drug, and inside the other compartment during conditioning session(s) with the drug vehicle. After typically several conditioning sessions, the allocation of time spent in the two compartments by the subjects is compared to that allocation before conditioning (Bardo and Bevins 2000; Tzschentke 1998; 2007). As shown by several research groups, this place conditioning increases the time allocation to the compartment associated with the injection of selected doses of abused drugs compared to little or no change with only vehicle injections. One advantage of the place conditioning procedure is that it is possible to detect both conditioned aversion and preference for the drug paired compartment.

Unfortunately, results for drugs belonging to the cannabinoid class (see Table 2) are not as straightforward as for other drug classes abused by humans (Tanda and Goldberg 2003). It is not uncommon for both conditioned preference and aversion to be reported for cannabinoids agonists (Tzschentke 1998). For example, the same doses of THC, injected at different time or pretreatment intervals, have been found to produce both preference and aversion in place-conditioning tests (Lepore et al. 1995; Valjent and Maldonado 2000). Moreover, failure to show conditioned preference with THC and other cannabinoid agonists has been repeatedly reported (Chaperon et al. 1998; Cheer et al. 2000; Mallet and Beninger 1998; McGregor et al. 1996; Sanudo-Pena et al. 1997). Most of these studies report a conditioned aversion produced by cannabinoid agonists, and two studies surprisingly show significant conditioned preference for a cannabinoid antagonist, rimonabant. This has been interpreted as evidence for the existence of a cannabinoid counter-rewarding system in the brain (Cheer et al. 2000; Sanudo-Pena et al. 1997), although other studies did not replicate those findings either with rimonabant (Chaperon et al 1998; Braida et al 2001, 2004), or with a different CB1 antagonist, AM251 (Scherma et al. 2008b).

Several factors, in particular pharmacokinetics, have been suggested to explain the contrasting results from place conditioning tests obtained with THC. When administered i.p. or orally THC has a slow onset and offset of effects, which might require that the conditioning session be exquisitely timed. Previous studies indicated that the onset of effects can depend on the vehicle used to solubilize THC, a factor that has been shown to play a role in its bioavailability (Carney et al. 1977; Mantilla-Plata and Harbison 1974; 1975; Ohlsson

et al. 1980; 1981). The duration of THC action is also influenced by its very high lipophilic profile which is likely prolonged as a result of slow dissociation from fat depots, prolonging its duration of action.

Lepore et al (1995) showed that when the THC conditioning sessions were conducted at intervals of 48 hours, lower doses of THC, 1 mg/kg, produced aversion, while higher doses, 2–4 mg/kg, produced place preference. However, when the experiments were conducted with THC conditioning sessions spaced 96 hours apart, lower doses induced place preference and higher doses produced aversion (see figure 2). The explanation offered for the different effects was that when time between THC conditioning injections does not allow the possible dysphoric actions to dissipate, the subsequent injections occurred during a dysphoric, non-hedonic state. Indeed, as suggested by the authors, low doses of THC might produce a dysphoric rebound measured by brain stimulation procedures that lasts for more than 48 hours (Lepore et al. 1996). A dose-dependent, biphasic and inverted U-shaped effect was obtained when doses of THC were administered every 96 hours (Lepore et al. 1995). Alternatively, we could explain the difference among these THC experiments as a leftward shift of the dose-response effects of THC when delaying the interval of THC injections from 48 to 96 hours. As can be seen in figure 2, the longer intervals between THC injections potentiate the preference- producing effects of smaller doses of THC, while increasing the aversive effects of larger doses. In order to minimize dysphoric effects that could interfere with the conditioning procedure, Valjent and Maldonado (2000) studied a conditioning procedure that revealed a place preference in THC conditioned mice. Mice were injected or primed non-contingently with a dose of THC the day before the start of the conditioning sessions. Under those conditions the authors observed place preference with low THC doses and neither preference nor aversion with higher doses that in non-primed mice produced place aversion (Valjent and Maldonado 2000).

Mechanisms for the place preference or aversion to cannabinoids have been studied in genetically engineered mice. In contrast to wild-type mice, dynorphin-deficient mice did not show THC conditioned aversion (Zimmer et al. 2001). Moreover, using the previously detailed THC-priming procedure (Valjent and Maldonado 2000), Gohzland et al (2002) showed that while THC-induced preference is under control of μ-opioid receptors, THC-induced aversion depends on κ-opioid receptors (see Table 2). THC has been shown to induce stimulation of extracellular levels of opioid peptides, for example, β-endorphins in the VTA (Solinas et al. 2004) and dynorphin-B in the spinal cord (Houser et al. 2000). Thus, genetic deletion of specific opioid receptors blunts the effectiveness of THC in producing specific effects mediated by those receptors. It is interesting to note that local injections of THC or cannabinoid agonists, given i.c.v. or directly into specific brain areas, VTA and accumbens shell, would produce place preference in rats (Braida et al. 2004; Zangen et al. 2006).

In addition, environmental factors can contribute to differences in the induction of preference or aversion, in place-conditioning studies. For example, WIN55212-2 has been shown to produce place preference in rats raised in an enriched environment, but not in a standard one (Gobbi et al. 2005).

In summary, as was seen with the ICSS procedures, cannabinoids do not produce consistent results in place-conditioning procedures. Both pharmacological and environmental factors may influence outcome. As with ICSS procedures, predicting abuse liability of novel cannabinoid drugs with results obtained through this procedure should be considered cautiously until we better understand all of the factors involved in the contrasting outcomes obtained with cannabinoids.

Neurochemistry

THC has been suggested to interact with several neurotransmitter systems (Acquas et al. 2000; Egashira et al. 2002; Gessa et al. 1998; Mishima et al. 2002; Pisanu et al. 2006), but in this section the focus will be mainly on the interactions of cannabinoids with dopamine (DA) neurochemistry. Indeed, the neurochemical, DAergic effects of THC have been another example of how to infer reinforcing effects of marijuana by comparing the effects of its main psychoactive ingredient, THC, with those produced by standard drugs of abuse (Pontieri et al. 1995; Pontieri et al. 1996; Tanda et al. 1997).

Most drugs of abuse produce a larger increase in extracellular DA levels in the nucleus accumbens as compared to that obtained in the dorsal striatum (Di Chiara et al. 1993a; Di Chiara et al. 1999; Koob 2000). Neuropharmacological and behavioral studies have also suggested that DA transmission in the nucleus accumbens plays a critical role in mediating the rewarding/reinforcing effects of drugs of abuse, and their abuse liability (Di Chiara et al. 1993a; Di Chiara and Imperato 1988), a relationship that we know today is more complicated (Di Chiara et al. 1998; Koob 1999). Detailed anatomical and histological studies of the shell and core sub-regions of the accumbens demonstrated regional differences in their input/output connectivity and in their basic functions, with the shell related to “limbic” functions and the core related to somato-motor functions (de Olmos and Heimer 1999; Di Chiara et al. 1993b; Heimer et al. 1991; Pontieri et al. 1995; Pontieri et al. 1996; Zahm and Heimer 1990; 1993). Table 3 shows the effects of several drug classes on stimulation of DA in the shell/core subdivisions of the accumbens in rodents, and the relation to self-administration behavior.

Early evidence that THC stimulates ventral striatal DA neurotransmission (Chen et al. 1993; Chen et al. 1990a; Chen et al. 1990b; Chen et al. 1991; Ng Cheong Ton et al. 1988) was accompanied by other reports in which no significant changes in DA levels were obtained in striatal areas (Castaneda et al. 1991; Chen et al. 1991). These contrasting results on THC-induced stimulation of DA transmission were mostly obtained in early studies when DA synthesis or levels of DA were determined ex vivo in brain slices or tissue that included striatal areas (Bloom and Dewey 1978; Bloom et al. 1978; Lew and Richardson 1981; Navarro et al. 1993; Rodriguez De Fonseca et al. 1992; Sakurai-Yamashita et al. 1989). Two factors seemed to play a role in whether or not THC stimulated DA in striatal areas: 1) the animal strain, as was also suggested for place preference and ICSS procedures; 2) brain region. For instance, significantly greater THC-induced increase in extracellular DA in the accumbens of Lewis compared to Sprague Dawley rats was reported (Chen et al. 1990b), and confirmed several years later (Cadoni and Di Chiara 2007; Tanda and Dichiara, Unpublished observations). However, after careful review of the available literature, it

appears that the stimulating effects of THC on DA transmission depend more on specific regional requirements, i.e. accumbens shell versus core or dorsal caudate, than on strain, as has been shown for other drugs of abuse (see Table 3). The assessment of pharmacological specificity of brain areas to THC effects on DA levels was reported (Tanda et al. 1997). In that study, the selective effects of THC on accumbens shell VS core DA levels were also mimicked by the CB1 agonist, WIN55,212-2, and blunted by pretreatments with the cannabinoid CB1 receptor antagonist, rimonabant. Further, using the same brain coordinates as in Tanda et al (1997), large increases in DA levels in the accumbens shell have been obtained with doses of THC up to 3 mg/kg i.p. (Justinova et al. 2013; Solinas et al. 2007a). Thus, lack of THC effects on DA levels in striatal areas reported in several studies might result from implanting the microdialysis probe in areas less responsive to THC effects, i.e. the caudate putamen or the accumbens core (Castaneda et al. 1991; Chen et al. 1990b; Chen et al. 1991; Tanda et al. 1997). In agreement with this regional specificity, Melis et al. (2000) showed THC-induced stimulation of firing in VTA DAergic neurons, which project to limbic DAergic terminal areas such as the accumbens shell. A similar neuronal firing enhancement by THC was not found in the substantia nigra pars compacta, which projects primarily on DA terminal fields such as the caudate-putamen or accumbens core. These experiments revealed a difference in regional brain sensitivity to THC effects in subpopulations of DA neurons, in agreement with the different change in DA levels among DA terminal areas (de Olmos and Heimer 1999; Tanda et al. 1997).

The studies by Melis et al (2000) confirmed the CB1 pharmacologic specificity of THC effects on DA by antagonism with rimonabant pretreatments, confirming also that rimonabant pretreatments did not affect heroin-induced stimulation of DA levels (Caille and Parsons 2006; Tanda et al. 1997). However, the nonselective opioid antagonist, naloxone, and the μ1-selective antagonist, naloxonazine that blocked both heroin and THC enhancement of DA levels (Chen et al. 1990b; Tanda et al. 1997), did not block the electrophysiological effects of THC on DA cell firing (French 1997; Melis et al. 2000). Several reasons may explain these different effects of opioid antagonists. It is possible that the different experimental conditions for freely-moving animals in microdialysis versus anesthetized or paralyzed animals in the electrophysiology experiments interacted with THC or opioids to produce different effects on neuronal firing. Alternatively the microdialysis experiment was performed with local VTA injections of naloxonazine, which may produce a more robust, area-selective effect than systemic injections. The antagonistic effects of naloxone and naloxonazine on THC-induced stimulation of DA would suggest blockade of effects exerted by endogenous VTA opioid peptides released by THC actions. As shown above, Dr. Goldberg's group reported THC-induced release of β-endorphins in the VTA (see Figure 1)(Solinas et al. 2004). Stimulation of opioid μ1 receptors in the VTA results in a reduction of GABA inhibitory effects on firing of DA neurons and, in turn, of DA release (Di Chiara and North 1992). This release of endogenous opioid peptides was functionally related to THC actions, since it was found capable to modulate THC subjective effects in rats trained to discriminate THC from vehicle (Solinas et al. 2004)(Figure 1).

Thus, endogenous opioids could play a role in the behavioral actions of THC and cannabinoids. Lately, endogenous ligands for cannabinoid receptors have been discovered. Researchers have explored the possibility that endocannabinoids that share with THC

affinity for CB1 receptors might participate to brain functions and pathways potentially related to reward. Recently, indeed, changes in nucleus accumbens shell DA transmission produced by endogenous cannabinoids have been reported (De Luca et al. 2014; Solinas et al. 2006). The increases in DA levels produced by anandamide and 2 AG parallel the findings on potential reinforcing effects of these drugs assessed in self-administration procedures (De Luca et al. 2014; Justinova et al. 2005b). These papers suggest that the endogenous cannabinoids activate reward-related brain structures and pathways producing reinforcing effects similarly to plant cannabinoids like THC.

It is worth noting that even though the reinforcing effects of THC have not been demonstrated in rodents, intravenous self-administration of a cannabinoid agonist, WIN 55,212-2, has been shown in rats and mice (Fattore et al. 2001; Lecca et al. 2006; Ledent et al. 1999; Martellotta et al. 1998). Additionally, increases in DA levels related to WIN 55,212,2 intake have been reported to be greater in the shell than in the core of the accumbens (see Figure 3) during the behavioral sessions of self-administration (Lecca et al. 2006). Further, the increase in DA measured by microdialysis was related to self-administration of the cannabinoid agonist, because during extinction (when receiving saline instead of WIN55,212-2), DA levels did not change despite continued but decreasing rates of responding. In more recent reports an increase in DA levels related to systemic administration and self-administration of the synthetic cannabinoid JWH018 (De Luca et al. 2015), known as “spice,” has been demonstrated in rats. Again, larger increases in extracellular DA levels have been reported in the shell as compared to the core of the accumbens, as a confirmation of potential for abuse (Table 3).

Preclinical studies on cannabinoids self-administration behavior in rodents and monkeys

With only a few exceptions, drugs of abuse are also self-administered by experimental animals, intravenously or orally (Katz and Goldberg 1988). In its simplest configuration, this behavioral procedure allows the animal to freely move inside a cage, to inject a drug or drink a solution of the substance, after specific behavioral requirements have been met (for details of the procedure see Spealman and Goldberg 1978). The most frequently employed intravenous self-administration procedure is one in which each response or a fixed number of responses (fixed-ratio or FR schedule) produces a drug injection. With the addition of a time-out, a signaled time during which responses have no consequences, following each injection, the pattern of responding maintained by drug injection is similar to patterns of responding maintained by more conventional reinforcers, such as food presentation (Goldberg 1973).

In contrast to other drugs of abuse, THC is not self-administered in rodents or rhesus monkeys, and has to date only been demonstrated in squirrel monkeys. The reasons why THC self-administration is not obtained in rodents and in rhesus monkeys is not definitively known. Several research groups have recently tested THC as a reinforcer in self-administration studies in rhesus monkeys or rats (Li et al. 2012; Scherma, Tanda and Goldberg, unpublished observation). Several factors have been taken into consideration to

provide a reasonable explanation for the unsuccessful attempts to obtain THC self-administration behavior in rodents and rhesus monkeys (Justinova et al. 2005a; Tanda and Goldberg 2003). In the next paragraphs, and in the Table 4, the procedures of unsuccessful attempts at THC self-administration in experimental animals are compared with those that were successful in squirrel monkeys. Three main factors will be compared and discussed: 1) the schedule of self-administration; 2) the doses and bioavailability of the drug; 3) the animal species

1. Schedule of self-administration

The self-administration behavior maintained by THC in squirrel monkeys was obtained using an FR 10 schedule (ten lever presses on the active lever produced an intravenous injection) of drug-delivery (Tanda et al. 2000), or using a second-order schedule of drug-delivery (Justinova et al. 2008) that will be discussed later in this section.

As shown in Table 4, different, and sometimes very complicated, schedules of drug injection or delivery have been tested in rhesus monkey. In early studies inhalation, oral or intravenous routes were unsuccessfully used to test THC or cannabis-related compounds (Amit et al. 1973; Corcoran and Amit 1974; Leite and Carlini 1974; Pickens et al. 1973). For example, in a report by Harris and coworkers (Harris et al. 1974), naïve and cocaine-experienced rhesus monkey were tested with THC under an FR schedule. Some tests were performed with delivery of intravenous mixtures of cocaine and THC, or after a month of exposure to response-independent programmed injections of 2 mg/kg of THC daily. None of those studies demonstrated reliable THC self-administration above levels maintained by vehicle injections.

Longer-term exposures to response-independent THC in monkeys have also been examined (Kaymakcalan 1973; Kaymakçalan 1972). The logic of this “pretreatment” evolved from earlier studies with other psychoactive agents (Deneau et al. 1969) in which self-administration of certain drugs in some naïve monkeys was only obtained after automatically programmed response-independent injections. After programmed injections two out of six monkeys self-administered THC at low rates (Kaymakcalan 1973; Kaymakçalan 1972).

In other reports monkeys were trained to self-administer drugs of abuse such as phencyclidine or cocaine. However THC failed to maintain behavior when substituted for these training drugs (Mansbach et al. 1994; Pickens et al. 1973). For example, the potent cannabinoid agonist, CP55,940, was substituted in rhesus monkeys trained to reliably self-administer phencyclidine by Mansbach and colleagues, (1994). Despite reliable phencyclidine self-administration, response rates above vehicle levels were not maintained by either THC or CP55,940. Similarly, THC failed to substitute in rhesus monkeys self-administering heroin (Li et al. 2012).

In the report by Tanda et al (2000) monkeys were trained with cocaine and tested with various drugs in cocaine experiments for longer than 1 year; these monkeys had at least one month of washout and 2 weeks of saline availability before they were assigned to the THC self-administration group. Cocaine training was thought to be a key factor in THC self-

administration in squirrel monkeys (Maldonado 2002). However, a subsequent demonstration of THC self-administration in drug-naïve squirrel monkeys, and the successful demonstrations of anandamide and methanandamide self-administration, again, in drug-naïve squirrel monkey, made it clear that cocaine training is not a necessary condition for acquisition of cannabinoid self-administration. Although self-administration of THC has not been found in other species, except for local brain injections of THC (Braida et al. 2004; Zangen et al. 2006), intravenous self-administration of other cannabinoid agonists, like WIN55212, 2-AG, JWH018 has been reported in rodents (De Luca et al. 2015; De Luca et al. 2014; Fattore et al. 2001; Lecca et al. 2006; Martellotta et al. 1998). This is of particular importance since the widespread use of new designer cannabinoids. Indeed, samples of "spice" blends, which is a new format of drugs of abuse on the street, have shown that several high affinity cannabinoid agonist are present in this abused substance (Debruyne and Le Boisselier 2015).

As shown in the Table 4, intravenous injections of THC also served as a reinforcer under second-order schedules of self-administration. Under these procedures the completion of one schedule requirement is treated as a unit of behavior that is in turn reinforced according to another schedule of reinforcement (Kelleher 1966). Often an exteroceptive stimulus is briefly presented at the completion of each of the "unit" schedules as well as at completion of the unit schedule that produces the reinforcer. The briefly presented stimulus can facilitate the maintenance of behavior such that an extended sequence of behavior is maintained before delivery of the reinforcer. For example, Goldberg et al. (1976) maintained responding of rhesus monkeys under an FI 60-min (FR 10:S) second-order schedule in which each completion of the FR 10 unit schedule produced a brief light illumination and the first completion of the FR 10 produced the brief visual stimulus and an injection of morphine, ending the experimental session for the day. Under this schedule, large numbers of responses were emitted, though concentrated towards the end of the hour, and importantly these responses occurred before drug was injected and therefore were not influenced by consequent intoxication. As indicated in the previous section, intoxication from large doses of THC may have interfered with a clear demonstration of reinforcing effects in the earliest studies (see also Carriero et al. 1998). Thus, a second-order schedule seemed a natural initial approach to studying reinforcing effects of THC, and was used in initial studies of THC self-administration, though those results were ultimately published later (Justinova et al. 2008)

Responding of squirrel monkeys under the second-order schedule was well maintained throughout the session and was characteristic of those performances previously maintained with other drugs or food reinforcement. In addition, rates of responding were related to dose with an inverted U-shaped function characteristic of dose-effects with other abused drugs. When the consequent THC injections were replaced with vehicle injections response rates decreased to low levels. Because all THC injections were delivered at the end of the experimental session the decreases in response rates were observed in the second session after THC was replaced with vehicle. When rimonabant (0.3 mg/kg) was administered before sessions, response rates immediately decreased to low levels before THC administration. Removal of the brief stimulus that followed FR unit schedule completions also immediately decreased rates of responding to very low levels. When the brief stimulus and THC were discontinued, reinstatement of responding was reliably obtained with

reintroduction of the brief stimulus only. Interestingly, this reinstatement was blocked by rimonabant injection. Further, after responding had been reduced by elimination of the brief stimulus and removal of the consequent THC injection it was reinstated with injections of THC, the endogenous cannabinoid anandamide (or its metabolic stable congener, methanandamide), the endocannabinoid uptake blocker AM404, morphine, and to a lesser degree by relatively high doses of cocaine.

Rimonabant also blocked THC-induced reinstatement but not morphine induced reinstatement, whereas naltrexone blocked morphine- but not THC-induced reinstatement, indicating that each antagonist specifically blocked the reinstatement of a behavior induced by the corresponding receptor specific agonist. The blockade by rimonabant was of considerable interest as it suggested CB1 receptor antagonism would not only block the reinforcing effects of THC but also the effects of stimuli associated with THC administration. This more global blockade suggests the potential of CB1 antagonism as a strategy to treat cannabis use disorder as well as all of the phenomena surrounding the conditioned effects of stimuli associated with THC abuse (Justinova et al. 2008). Unfortunately rimonabant for human use has been discontinued and suspended due to severe psychiatric side effects (E.M.A. 2008). However, the study of neutral antagonists of CB1 receptors, as opposed to the antagonist/inverse-agonist rimonabant, is an important area for future research and suggests it may be possible to reduce THC reinforcing effects without unwanted psychiatric side-effects.

2. Doses and bioavailability of the drug

In review of the unsuccessful tests of THC self-administration in experimental animals, the majority of papers used i.v. THC doses as high as 0.2-0.4 mg/kg/inj. Several studies report that subjects were intoxicated after the session, even with the delivery of only a few THC injections at a frequency not greater than that for vehicle (Harris et al. 1974; Mansbach et al. 1994; Pickens et al. 1973). In contrast, the first successful studies with THC self-administration used THC doses that ranged from 1 to 16 μg/kg/injection (Justinova et al. 2003; Tanda et al. 2000). With those doses the squirrel monkeys when observed post-session did not show signs of intoxication. Further, in the few “almost successful” earlier attempts at establishing THC self-administration, doses of THC were in the low microgram range (Takahashi and Singer 1979; 1980; 1981). Thus, most of the unsuccessful attempts to obtain self-administration of THC used doses of THC much higher than those subsequently shown to be effective in squirrel monkeys.

That the dose-range examined is a critical factor for THC self-administration is not unexpected as it is important for all pharmacological actions. However, an important question is how the doses used relate to those used by humans. In the study by Tanda et al (2000) the total i.v. intake of THC obtained by monkeys ranged from 50 to 120 μg/kg over a one-hour session at doses of 2 and 4 μg/kg/injection. In a clinical study (Ohlsson et al. 1981), i.v. injection of 5 mg of THC (~70 μg/kg) produced the same degree of "high" as that reported by humans after smoking marijuana or hashish. That ~70 μg/kg dose is similar to the total intake of THC self-administered by squirrel monkeys.. Further, as THC bioavailability from smoking marijuana is on average about 20% (Agurell et al. 1986), the

actual THC intake would be about 3 mg in human subjects smoking a cigarette containing 15 mg of THC. Distributed over 10 to 15 puffs, each puff would contain 200 to 300 μg of THC or approximately 2.9 to 4.3 μg/kg of THC delivered per puff. This dose per puff is in good agreement with the range of injection doses (2 to 4 μg/kg) that maintained responding in the squirrel monkey self-administration studies.

Bioavailability likely also plays a role in the reinforcing effects of THC. THC is usually commercially available as an ethanol solution, since it is practically insoluble in water. Several reports describe THC solutions for intravenous injections in vehicles that kept the compound in suspension, with obvious limits to bioavailability, even when injected i.v.. In the study by Tanda et al (2000) THC was dissolved in a tween 80/ethanol/saline vehicle, using a modification of the procedure described by Olsen et al (1973). This vehicle provides a rapid distribution of THC to different tissues, especially the brain, compared to other commonly employed vehicles (Mantilla-Plata and Harbison 1975). This vehicle was selected based on its previous use in a study in which THC was injected intravenously and significantly elevated DA levels in the shell of the nucleus accumbens of the rat during the first 10 to 20 minutes after injection (Tanda et al. 1997). This effect on DA, which resembles that produced by heroin, cocaine, or amphetamine, appears critical for addictive behaviors (Di Chiara et al. 1999; Koob et al. 1998).

3. Animal species

We know from previously cited studies in rats that genetic background can have a profound impact in the effects of THC and other cannabinoid agonists in place preference, brain self-stimulation and DA microdialysis procedures. What we do not know, yet, is whether squirrel monkeys, like human subjects, have the ability to self-administer THC because of specific genetic/physiologic determinants or differences in metabolism/pharmacokinetics from other species. It remains possible that the best THC self-administration conditions for other species simply have not yet been found. Interestingly, the same squirrel monkeys used to establish THC self-administration by Tanda et al. (2000) had been used previously without success using a similar THC i.v. dose range but with a different vehicle (Poly-Vinyl-Pyrrolidone) (S. Yasar and S. Goldberg, unpublished observations). It is worth noting that nicotine self-administration has similarly been found to be effective in the squirrel monkeys (Goldberg et al. 1981), when its reinforcing effects in other species were inconsistently obtained (Stolerman and Jarvis 1995).

Thus, it is likely that several factors play a role in the difficulty to find the best experimental conditions for studying the potential reinforcing effects of cannabinoids in different animal species. Even trying to “reverse translate” human behaviors, related to abuse of substances, to animals does not seem to help. For instance, most of the self-administration studies using FR 1 schedules (one injection for each response) show a pattern with multiple drug injections, which might seem at variance with the pattern of drug intake shown by human subjects abusing drugs like heroin or cocaine, usually taken in limited amounts, often once per day, thus with drug use not really distributed over time. So, it is worth noting that drugs like nicotine or marijuana, often smoked and with a pattern of intake distributed more broadly over time, as in self administration sessions, have been among the most refractory to

the establishment of robust self-administration in animals. Nicotine self-administration has ultimately been documented in squirrel monkeys, baboons, rats and mice, though only under specific procedural conditions (Ator and Griffiths 1983; Caggiula et al. 2002; Caggiula et al. 2001; Corrigall 1999; Goldberg and Henningfield 1988; Henningfield and Goldberg 1983). Thus, as with nicotine (Stolerman and Jarvis 1995), it is possible that the necessary conditions for more widespread success in the study of reinforcing effects of THC are soon to be better documented.

Conclusions

Several behavioral procedures have been reviewed here in an attempt to understand how the potential for abuse of cannabis derivatives could be studied using indirect assessments of their reinforcing actions. Inconsistency of results obtained with place conditioning and ICSS procedures suggest that drug-discrimination and neurochemistry are the best indirect predictors of cannabinoid-like pharmacology and abuse liability of new cannabinoid compounds, respectively.

Since the first paper reliably demonstrating reinforcing effects of THC was published in the year 2000, the THC self-administration model of marijuana abuse has provided the possibility of directly studying reinforcing effects and abuse liability of THC as well as other cannabinoid agonists. That study and those that followed showed that like THC, the endogenous brain cannabinoids, anandamide and 2AG, are self-administered. These results suggest an important involvement of brain endocannabinoid systems in the central mechanisms of reinforcement. Self-administration procedures have also been of paramount importance for evaluating pharmacological treatments as therapies for cannabis use disorders (Justinova et al. 2013; Justinova et al. 2004). Reliable THC self-administration allows the testing of potential medications for THC abuse to be realized in a manner that has substantial experimental utility. With new research from pharmaceutical companies on cannabinoids to treat pain (Kirkpatrick et al. 2015; Maione et al. 2013; Vemuri and Makriyannis 2015) their testing for abuse liability will be facilitated by self-administration models. New pain therapies are particularly important today with prescription opioid abuse reaching epidemic proportions; however there are a host of other potential therapeutic applications for cannabinoids. The availability of the squirrel monkey model of THC self-administration behavior will allow the development of new compounds with confidence in safety testing regarding their potential for abuse.

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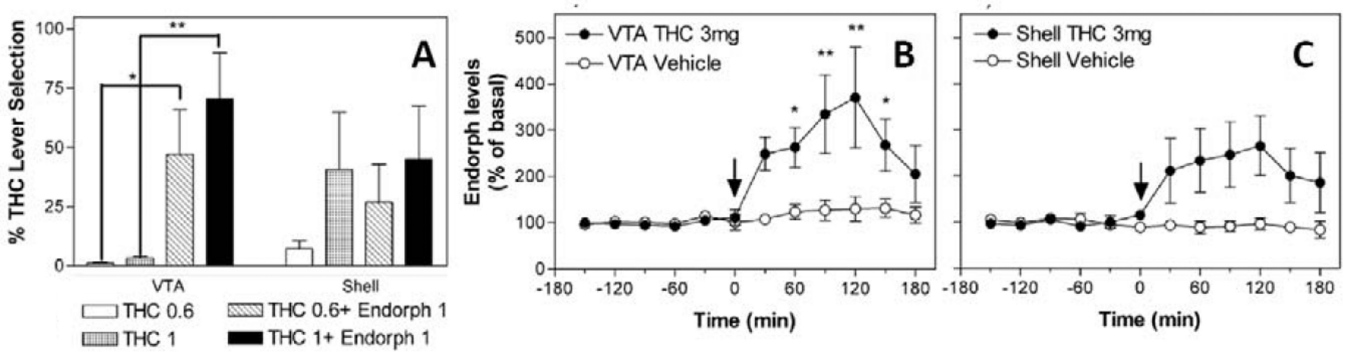

Figure 1. β-endorphins in the VTA mediate central THC actions

Panel A shows that local intra VTA, but not intra-accumbens shell, injections of β-endorphins potentiate the discriminative effects of small doses of THC, measured by % increase in THC appropriate lever selection, in rats trained to discriminate the subjective effects of THC 3 mg/kg i.p. from THC-Vehicle i.p. **Panels B and C** show that administration of THC, 3 mg/kg i.p., but not its vehicle, stimulates β-endorphin levels in dialysates from the VTA but not significantly from the accumbens shell. Modified from Solinas et al 2004. See text and the original article for more details about experimental procedures and results.

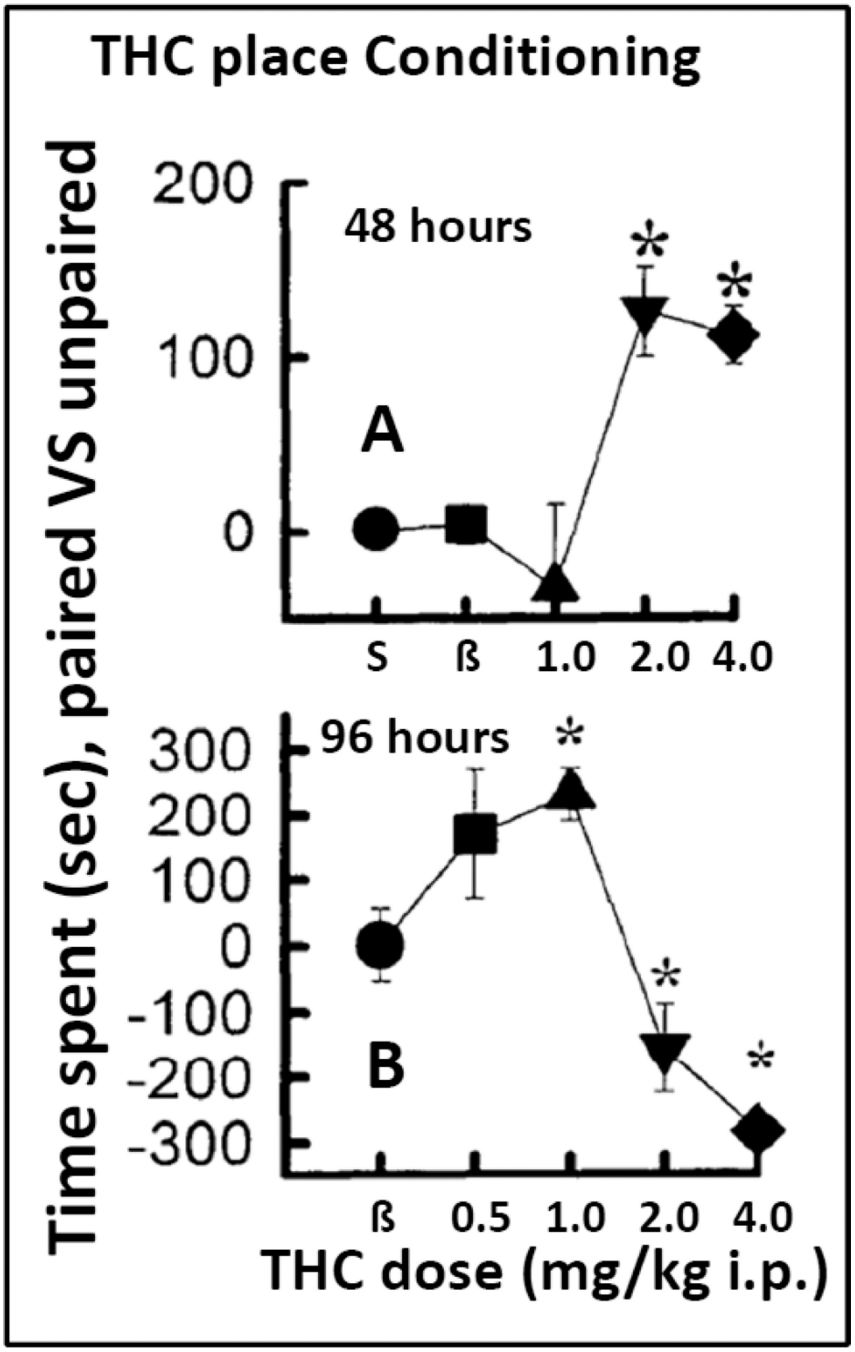

Figure 2. Effects of changing the time between THC sessions on place conditioning

Panel A shows effects of THC when conditioning sessions with THC were conducted 48 hours apart. Potential dysphoric effects of THC were hypothesized to reduce the likelihood of place preference at low THC doses (1 mg/kg i.p.). In **Panel B** with 96 hours between THC injections, there was a significant place preference at 1 mg/kg i.p., but also place aversion at higher doses. Modified from Lepore et al 1995. See text and the original article for more details about experimental procedures and results.

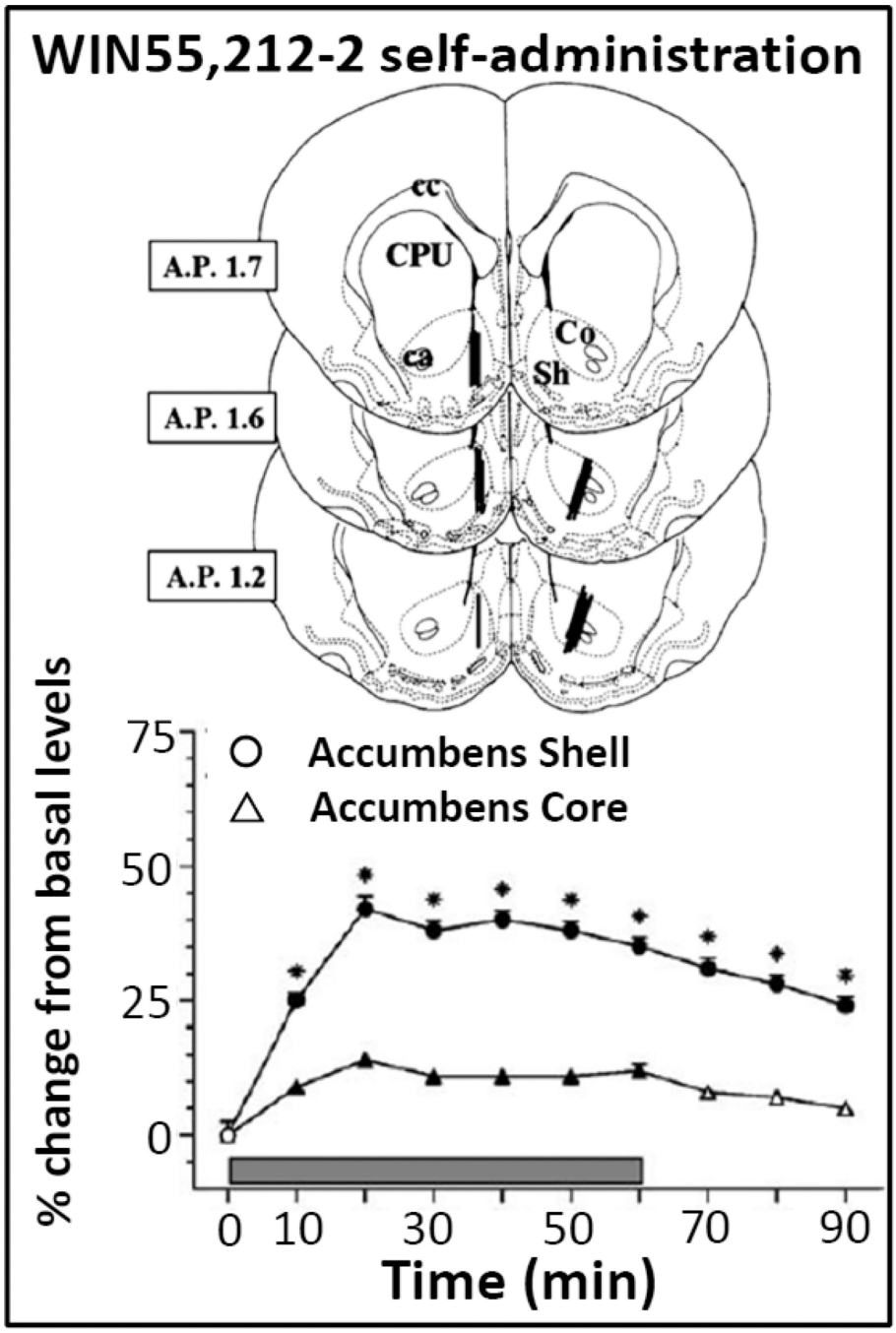

Figure 3. Neuroanatomical probe placements and neurochemical effects of WIN55,212-2 self-administration in Sprague-Dawley rats

Top Panel. Schematic drawings showing the location of microdialysis probes in the nucleus accumbens shell or core in rats self-administering WIN55,212-2 (12.5 μg/kg/infusion).

Bottom panel shows the time course of changes from basal DA levels in dialysates from the shell and core of the nucleus accumbens in rats during 4 weeks (12 sessions) of WIN55,212-2 self-administration. Modified from Lecca et al 2006. See text and the original article for more details about experimental procedures and results.

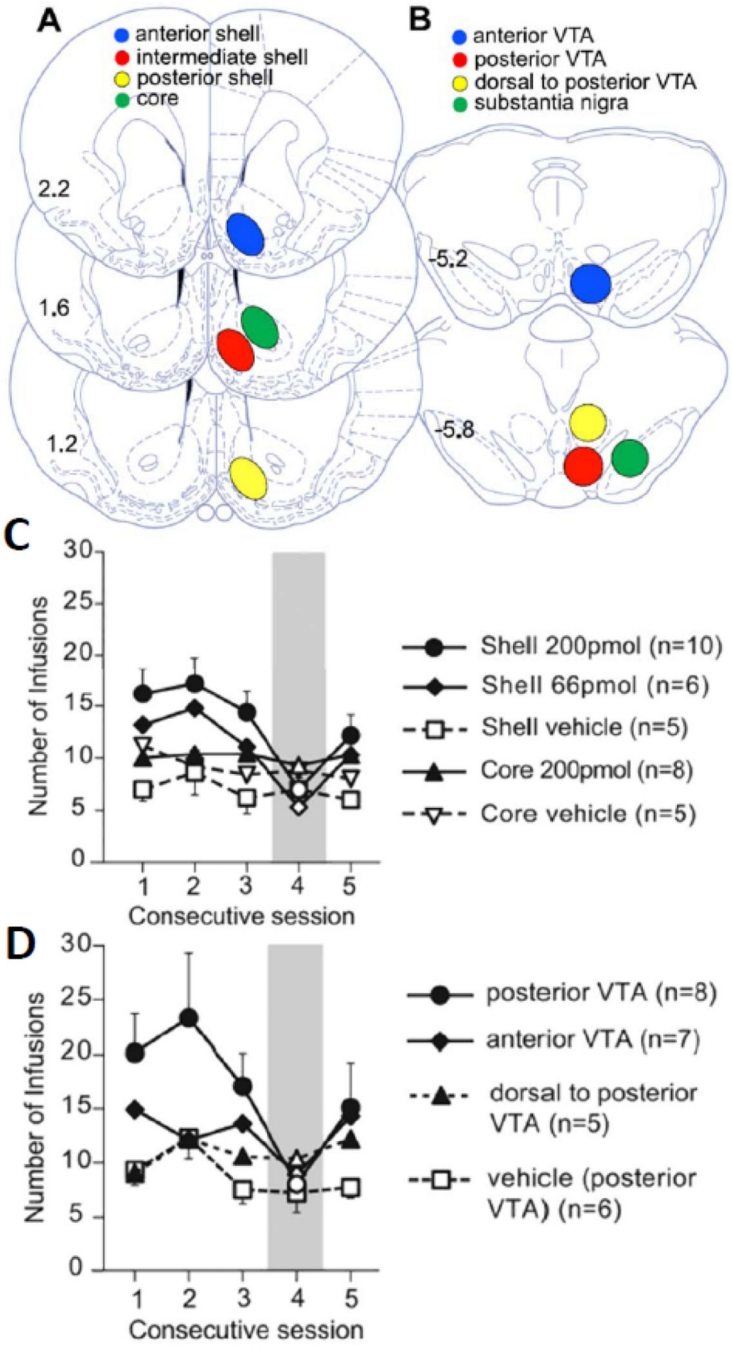

Figure 4. Neuroanatomical location of THC injections and number of self-infusion of THC in the shell or VTA as a function of daily sessions

Top panels (A and B) show the location of THC site infusions in the anterior, intermediate or posterior shell, or in the core, and in the anterior, posterior, or dorsal to posterior VTA, or in the substantia nigra. **Panels C and D** show the number of self-infusions of THC into different accumbens (C) or midbrain (D) sites, earned by rats during consecutive sessions. Session number 4 was characterized by substitution of THC by its vehicle. Modified from

Zangen et al, 2006. Please see text or the original article for more details about experimental procedures and results..

Table 1

Specificity of the subjective effects of cannabinoids under Drug Discrimination procedures.

References	Training drug, dose-range, (mg/kg) & route #	Test Drug, dose-range (mg/kg), route #	Species, Procedure ($), schedule	Result, % DLR
NON CANNABINOID DRUGS OF ABUSE				
(Solinas et al. 2010)	THC, 3.0	Amphetamine 0.3–1.8	Male, SD rats, TL, FR10	<20
(Browne and Weissman 1981)	THC, 3.2	Amphetamine 0.32	Male, SD rats, TL, FR10, CS–reinforced	0
(Jarbe and Henriksson 1974)	THC 5.0	Amphetamine 2.5–5.0	Male, SD rats, T-shaped water maze, escape reinforced	No substitution
(Solinas et al. 2010)	THC, 3.0	Cocaine 1–10	Male, SD rats, TL, FR10	<20
(Jarbe and Henriksson 1974)	THC 5.0	Cocaine 5–20	Male, SD rats, T-shaped water maze, escape reinforced	No substitution
(McMahon et al. 2008)	THC, 10.0	Cocaine, 10–56	Male C57BL/6J mice, TH, FR30, CM-reinforced	<25
(Wiley et al. 1995b)	THC, individual doses, 0.04–0.17 IM	Diazepam 0.025–1.2	Rhesus monkeys, TL, FR50,	31
(Mokler et al. 1986)	THC, 3.0	Diazepam 0.1–10	Male, SD rats, TL, FR10, SM–reinforced	60
(Jarbe and Henriksson 1974)	THC 5.0	Ethanol, 1000–2000	Male, SD rats, T-shaped water maze, escape reinforced	No substitution
(Jarbe et al. 2010)	THC, 1.8 or Methanandamide 10.0	Ethanol, 300–1000	Male, SD rats, TL, FR10	<48 and <40
(McMahon et al. 2008)	THC, 10.0	Ethanol, 320–1000	Male C57BL/6J mice, TNP, FR30, CM-reinforced	<25
(McMahon et al. 2008)	THC, 10.0	Ketamine, 3.2–32	Male C57BL/6J mice, TH, FR30, CM-reinforced	<25
(Browne and Weissman 1981)	THC, 3.2	LSD, 0.1	Male, SD rats, TL, FR10, CS–reinforced	8
(Jarbe and Henriksson 1974)	THC, 5.0 or Hashish smoke	Morphine 1.25–10.0	Male, SD rats, T-shaped water maze, escape reinforced	No substitution
(Wiley et al. 1995b)	THC, individual doses, 0.04–0.17 IM	Morphine, 0.1–1.0	Rhesus monkeys, TL, FR50,	0
(Browne and Weissman 1981)	THC, 3.2	Morphine, 3.2	Male, SD rats, TL, FR10, CS–reinforced	20
(Wiley et al. 1995b)	THC, individual doses, 0.04–0.17 IM	Phencyclidine 0.03–0.3	Rhesus monkeys, TL, FR50,	0
NATURAL AND SYNTHETIC CANNBINOIDS				
(Wiley et al. 1995a)	THC, 3.0	Anandamide, 30	Male, SD rats, TL, FR10	80
(Wiley et al. 1997)	THC, individual doses, 0.08–0.16 IM	Anandamide, 0.1–10.0	Rhesus monkeys, TL, FR50–100,	Not consistent
(Burkey and Nation 1997)	THC, 2.0	Anandamide, 0.5–16.0	Male, SD rats, TL, FR10, SW	<40
(Jarbe et al. 2001)	THC 1.8–5.6	Anandamide, 10–18	Male, SD rats, TL, FR10	0–21
(Jarbe et al. 2001)	Methanandamide, 10.0	Anandamide, 10–18	Male, SD rats, TL, FR10	85

References	Training drug, dose-range, (mg/kg) & route #	Test Drug, dose-range (mg/kg), route #	Species, Procedure ($), schedule	Result, % DLR
(Browne and Weissman 1981)	THC, 3.2	Cannabidiol, 10–32.0	Male, SD rats, TL, FR10, CS–reinforced	25
(Browne and Weissman 1981)	THC, 3.2	Cannabinol, ED50 6.77	Male, SD rats, TL, FR10, CS–reinforced	100
(Burkey and Nation 1997)	THC, 2.0	CP 55,940, 0.05–0.8	Male, SD rats, TL, FR10, SW	90
(Jarbe and Henriksson 1974)	THC 5.0 or Hashish smoke	Hashish smoke	Male, SD rats, T-shaped water maze, escape reinforced	100
(Burkey and Nation 1997)	THC, 2.0	Methanandamide, 0.5–8.0	Male, SD rats, TL, FR10, SW	90
(Jarbe et al. 2001)	THC 3.0	Methanandamide, 10–18	Male, SD rats, TL, FR10	80–100
(Wiley et al. 1995c)	THC, 3.0	Rimonabant, 0.3–5.6	Male, SD rats, TL, FR10	0
(Jarbe et al. 2001)	Methanandamide, 10.0	THC, 0.1–3.0	Male, SD rats, TL, FR10	100
(Jarbe 1982)	Amphetamine, 1.6 IM	THC, 0.125–0.5	Male, mixed strains, pigeons	<20
(Jarbe 1984)	Cocaine, 3.0 IM	THC, 0.3 IM	Male, White Carneaux pigeons, two keys, FR15	<16
(Wiley et al. 1995c)	THC, 3.0	WIN55,212–2, 0.1–3.0	Male, SD rats, TL, FR10	100
SYNTHETIC ABUSED CANNABINOIDS FOUND IN SEIZED SPICE-LIKE BLENDS				
(Gatch and Forster 2014)	THC, 3.0	JWH018 (AM678), 0.03-1	Male, SD rats, TL, FR10	
(Jarbe et al. 2010)	THC, 1.8 or methanandamide 10	JWH018 (AM678), 0.03-1	Male, SD rats, TL, FR10	100
(Gatch and Forster 2014)	THC, 3.0	JWH073, 0.1–10	Male, SD rats, TL, FR10	100
(Gatch and Forster 2014)	THC, 3.0	JWH200, 0.1–10	Male, SD rats, TL, FR10	100
(Gatch and Forster 2014)	THC, 3.0	AM2201, 0.03-1	Male, SD rats, TL, FR10	100

#intraperitoneal route of administration, unless indicated otherwise

$unless differently indicated, food was delivered as a reinforcer

IM=intramuscular route of administration
DLR=drug-lever responding
TL=two lever choice
TNP=Two nose-poke holes available
SD=Sprague Dawley rats
FR=fixed ratio
CM=condensed milk (50%) in tap water
CS=carnation slender diluted 1:1 to water
SM=sweetened milk
SW=saccharin (0.4%) in water
ED50=dose at which 50 of subjects responded to the drug lever

Table 2

Results from place conditioning tests with cannabinoid drugs.

Reference	Test Drug	Dose (mg/kg) and route (#)	Pretreatment time (min)/ session time (min)/number of exposures	time (hours) between drug injections	Species, strain/ Bias procedure?	Result
(Lepore et al. 1995)	THC	1.0.	20/30/3	48	Male, Long Evans rats/Unbiased	A
		2.0, 4.0		48		P
		0.5	20/30/3	96	Male, Long Evans rats/Unbiased	NS
		1.0		96		P
		2.0, 4.0		96		A
(Parker and Gillies 1995)	THC	0.2–1.5	5/30/3	72	Male, Spraue Dawley rats/Unbiased	NS
		0.2–1.5	5/30/3	72	Male, Lewis rats/Unbiased	NS
(McGregor et al. 1996)	CP 55,940	10	0/30/4	24	Male, Wistar rats/Unbiased	A
		100				A
(Sanudo-Pena et al. 1997)	THC	1.5	0/30/2	24	Male, Sprague Dawley rats	NS
		15				A
	Rimonabant	0.5	0/30/2	24		P
		5.0				P
(Mallet and Beninger 1998)	THC	0.1, 0.5	30/30/4	48	Male, Wistar rats/Unbiased	NS
		1.0, 1.5				A
		2, 4, 8				NS
	Anandamide + PMSF(*)	0.031–16	5/30/4	48		NS
(Chaperon et al. 1998)	WIN55,212–2	0.003–1	15/30/4	24	Male, Wistar rats/Unbiased	A
	Rimonabant	0.3–3	30/30/4	24		NS
(Cheer et al. 2000)	THC	1.5	10/10/3	24	Male, Lister Hodded rats/Unbiased	A
	Rimonabant	0.25–3	10/10/3	24		P
	HU210	0.02–0.1	10/10/3	24		A

Reference	Test Drug	Dose (mg/kg) and route (#)	Pretreatment time (min)/ session time (min)/number of exposures	time (hours) between drug injections	Species, strain/ Bias procedure?	Result
(Valjent and Maldonado 2000)	THC	1.0	0/45/5	24	Male, CD1 mice/Unbiased	NS
		5.0				A
	THC(***)	1.0	0/45/5	24		P
		5.0				NS
(Zimmer et al. 2001)	THC	5.0	0/45/ 5	24	wild type C57BL/6J mice; unbiased	A
		5.0	0/45/5	24	Dynorphin-deficient mice /Unbiased	NS
(Ghozland et al. 2002)	THC	1.0	0/45/5	24	Hibrid mice, 1:1 129sv and C57BL6/Unbiased	NS
		5.0				A
		1.0($)	0/45/5	24	Hibrid mice, 1:1 129sv and C57BL6/Unbiased	P
		5.0($)				NS
		1.0($)	0/45/5	24	μ-opiod-R KO mice/Unbiased	NS
		5.0($)				NS
		1.0	0/45/5	24	κ-opiod-R KO mice/Unbiased	P
		5.0				NS
		1.0($)	0/45/5	24	κ-opiod-R KO mice/Unbiased	P
		5.0($)				NS
		1.0($)	0/45/5	24	δ-opiod-R KO mice/Unbiased	P
		5.0($)				A
(Braida et al. 2001a)	CP55,940	0.02	10/30/4	48	Male, Wistar rats/Biased	P
	Rimonabant	0.5				NS
(Braida et al. 2004)	THC	0.015	10/30/4	48	Male, Wistar rats/Unbiased	NS
		0.075–0.75				P
		1–3				NS
		6.0				A
	Rimonabant	0.25–1.0,				NS

Reference	Test Drug	Dose (mg/kg) and route (#)	Pretreatment time (min)/ session time (min)/number of exposures	time (hours) between drug injections	Species, strain/ Bias procedure?	Result
(Le Foll et al. 2006)	THC	0.01	10/30/5	24	Male, Sprague Dawley rats/Unbiased	NS
		0.1				P
		1., 2.0				NS
(Scherma et al. 2008a)	Anandamide	0.3–3 i.v.	0/20/3	24	Male, Sprague Dawley rats/Unbiased	NS
	Anandamide + URB597 (*)	0.3–3.0 i.v.				A
	WIN55,212–2	0.05–3 i.v.				A
	AM251	3.0				NS

#if not specified, the intraperitoneal route was used.

A=conditioned place aversion
P=conditioned place preference

*PMSF and URB597 are inhibitors of the FAAH enzyme, and animals have been pretreated these drugs before anandamide to reduce a rapid anandamide metabolism.

**Even if rats received saline or Rimonabant at the end of each THC session, there was no change in the results for THC effects at 1 or 5 mg/kg i.p.

***Animals received a non-contingent injection of THC 24 hours before the first THC conditioning session. This treatment led to preference for the THC low dose and changed from aversion to NS the effects of the higher THC dose, independently form the Rimonabant pretreatment provided at the end of each THC session.

$Animals received a non-contingent injection of THC 24 hours before the first THC conditioning session.

Table 3

Drug-induced changes in DA levels in brain dopaminergic terminal areas and relationship with self-administration behavior.

References	Drug, dose (mg/kg), route	Microdialysis brain area. Effects on Dopamine levels	
		Rat NAC Shell DA	Rat NAC Core DA
PSYCHOSTIMULANTS			
(Pontieri et al. 1995, and unpublished)	**Cocaine, 0.5-1.0 IV**	INCREASE ↑	INCREASE
(Pontieri et al. 1995)	**Amphetamine, 0.125-0.25, IV**	INCREASE ↑	INCREASE
(Cadoni et al. 2005)	**MDMA, 0.64-2.0, IV**	INCREASE ↑	INCREASE
(Tanda et al. 2013)	**4'-4"-diChloro-BZT, 3-10, IP**	INCREASE	INCREASE
OPIOIDS			
(Tanda et al. 1997)	**Heroin, 0.018-0.032, IV**	INCREASE ↑	INCREASE
(Pontieri et al. 1995)	**Morphine, 0.2-0.4, IV**	INCREASE ↑	INCREASE
CANNABINOIDS			
(Tanda et al. 1997)	**THC 0.15-0.3 IV**	INCREASE ↑	NO EFFECTS
(Tanda et al. 1997)	**WIN55,212-2, 0.15-0.3, IV**	INCREASE ↑	NO EFFECTS
(Solinas et al. 2006)	**Anandamide 0.3-10.0, IV**	INCREASE	NOT TESTED
(Solinas et al. 2006)	**Methanandamide 0.3-10.0, IV**	INCREASE	
(De Luca et al. 2014)	**2-AG, 0.1-1.0, IV**	INCREASE ↑	NO EFFECTS
(De Luca et al. 2015)	**JHW018, 0.125-0.5, IP**	INCREASE ↑	NO EFFECTS
OTHER DRUGS OF ABUSE			
Pontieri 1996	**Nicotine, 0.025-0.05 IV**	INCREASE ↑	NO EFFECTS
Tanda unpublished	**Ethanol, 0.002-0.008, IV**	INCREASE ↑	NO EFFECTS
ANTIDEPRESSANTS			
(Tanda et al. 1994, and unpublished)	**Fluoxetine, 10-20, IP**	NO EFFECTS	NO EFFECTS
(Tanda et al. 1994); (Di Chiara et al. 1992)	**DMI 10-20, IP**	NO EFFECTS	NO EFFECTS
(Tanda et al. 1996)	**Mianserin, 1-10, SC**	DECREASE	NOT TESTED
ANTIPSYCHOTICS			
(Tanda et al. 2015)	**Haloperidol, 0.006-0.025, IV**	INCREASE	INCREASE
(Tanda et al. 2015)	**Chlorpromazine, 0.25-0.5, IV**	INCREASE	INCREASE

(Tanda et al. 2015)	**Clozapine, 1.0-2.0, IV**	INCREASE ↑	NO EFFECTS
(Tanda et al. 2015)	**Risperidone 0.05-0.1, IV**	INCREASE ↑	INCREASE
(Tanda et al. 2015)	**Raclopride, 0.025-0.075, IV**	INCREASE	INCREASE
ANXIOGENIC			
(Bassareo et al. 1996); Tanda, unpublished	**Picrotoxin, 0.5-1.0, SC**	NO EFFECTS	NO EFFECTS
(Bassareo et al. 1996); Tanda, unpublished	**Pentylentetrazol, 10-20, IP**	NO EFFECTS	NO EFFECTS
ANXIOLYTIC			
(Finlay et al. 1992); Tanda, unpublished	**Midazolam, 0.025-0.1, IV**	DECREASE	NO EFFECTS
OTHER DRUG CLASSES			
(Tanda et al. 2008)	**Triprolidine, 1.0-3.0, IV**	NO EFFECTS	NO EFFECTS
(Tanda et al. 2008)	**Diphenhydramine, 1.0-3.0, IV**	INCREASE ↑	INCREASE
(Chen et al. 2015; Tanda et al. 1996)	**Yohimbine, 1.0, 5.0, IP**	NO EFFECTS	NO EFFECTS
(Acquas et al. 2002)	**Caffeine, 0.25-5.0, IV**	NO EFFECTS	NO EFFECTS

DA= dopamine; ↑=significantly different from NAC core DA; IV=intravenous administration; IP= intraperitoneal administration; SC = subcutaneous administration.

Shadowed cells indicate that self-administration behavior is maintained by the drug in experimental animals.

Table 4

Self-Administration behavior, tests with cannabinoid drugs

Reference	Drug reinforcer. Dose and vehicle	Species	Procedure/schedule	Main Results
T H C				
Deneau and kaymakcalan 1971; Harris et al. 1974	100–400 μg/kg Tween20/salineine or 25–300 μg/kg PVP/saline	Rhesus monkeys	IVSA, FR1, naïve subjects	No significant acquisition
Mansbach et al. 1994; Pickens et al. 1973	17–100 μg/kg in PVP/saline or EL620/EtOH/saline		IVSA, FR1, Substitution for phencyclidine	No significant substitution
Carney et al. 1977; Harris et al. 1974; Kaymakcalan 1973	3–300 μg/kg EL620; 25–200 μg/kg PVP/saline;100–400 μg/kg Tween20/saline		IVSA, substitution for cocaine	No significant substitution
Harris et al. 1974	25–300 μg/kg PVP/saline		IVSA, cocaine/THC combinations. Automated programmed delivery	No significant acquisition/substitution
Kaymakcalan 1973	100–400 μg/kg Tween20/saline		IVSA, Monkeys made dependent on THC	No significant acquisition (2 out of 6)
Pickens et al. 1973	25 mg burned hashish		Inhalation and food presentation/FR3 and 4 sec. mouth contact to smoke tube, 24 hours per day, 4 days each week	No significant difference from vehicle responding
Li et al. 2012	3.2–32 μg/kg EL620/EtOH/saline		IVSA, history of heroin SA or naive	No significant acquisition
Corcoran and Amit 1974	0.25 mg (hashish)/ml	Rats	Forced drinking	No significant acquisition
van Ree et al. 1978	7.5–300 μg/kg tween20/saline		IVSA, naïve	40% positive
Takahashi and Singer 1979; 1980	6.25–50 μg/kg tween80/saline		IVSA, naïve, food deprived, with automatic food pellet delivery	Positive results maintained only with food deprivation and pellet delivery
Braida et al. 2004	0.01–1 μg/inf cerebrospinal fluid, EtOH, cremophor		ICVSA, trained with water	Positive results, max responding at 0.02 μg/inf
Tanda et al. 2000; Justinova et al. 2008; Justinova et al. 2003	1–16 μg/kg EtOH/Tween80/saline	Squirrel monkeys	IVSA, naïve or cocaine trained with saline extinction/FR or second order	Positive results, max responding at 4 μg/kg
Anandamide and Methanandamide				
Justinova et al. 2005	2.5–160 μg/kg tween80/saline/eth	Squirrel monkeys	FR10, IVSA, drug naïve	Positive results, max responding at 40 μg/kg
2-AG				
De Luca et al. 2014	12.5–50 μg/kg tween80/saline/eth	Sprague Dawley Rats	IVSA, naïve	90% positive, max responding at 25 μg/kg
Justinova et al. 2011	0.1–100 μg/kg EtOH/Tween80/saline	Squirrel monkeys	IVSA, nicotine substitution or history IVSA of anandamide, anandamide reuptake inhibitors or nicotine	100% positive, max responding at 3 μg/kg
CP55,940				
Mansbach et al. 1994	0.3–3 μg/kg emulphor/ EtOH/saline	Rhesus monkey	IVSA,PCP substitution	No acquisition

Reference	Drug reinforcer. Dose and vehicle	Species	Procedure/schedule	Main Results
Braida et al. 2001	0.1–1.6 μg cerebrospinal fluid, EtOH, cremophor	Wistar Rats	IVSA	Positive, max responding at 0.4 μg/kg
WIN55,212-2				
Martellotta et al. 1998	10–500 μg/kg ?	CD1 Mice	IVSA, naïve	Positive, max responding at 100 μg/kg
Fattore et al. 2001	6.25–50 μg/kg Tween 80/heparin/saline	Wistar Rats	IVSA, naïve	87% positive, max responding at 12.5 μg/kg
Solinas et al. 2007	12.5–25 μg/kg Tween 80/saline	Long–Evans Rats		Positive, max responding at 12.5 μg/kg
Justinova et al 2013	12.5 μg/kg Tween- 80/heparin/saline	Long–Evans Rats/Sprague Dawley	IVSA, naïve	Positive
Lecca et al. 2006	12.5 μg/kg Tween 80/saline	Sprague Dawley Rats	IVSA, naïve	Positive
JWH 018				
De Luca et al. 2015	10–20 μg/kg EtOH/Tween80/saline	Sprague–Dawley Rats	IVSA, naïve	90% positive, max responding at 20 μg/kg
De Luca et al. 2015	15–30 μg/kg EtOH/Tween80/saline	C57BL/6 mice	IVSA, naïve	90% positive, at 30 μg/kg

IVSA = intravenous self-administration