HHS Public Access

Author manuscript

Behav Pharmacol. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

Behav Pharmacol. 2022 April 01; 33(2-3): 63–89. doi:10.1097/FBP.0000000000000592.

Translational models of cannabinoid vapor exposure in laboratory animals

Catherine F. Moore[1], **Jeffrey W. Stiltner**[1], **Catherine M. Davis**[1], **Elise M. Weerts**[1,*]

[1]Division of Behavioral Biology, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD.

Abstract

Cannabis is one of the most frequently used psychoactive substances in the world. The most common route of administration for cannabis and cannabinoid constituents such as –9-tetrahydrocannabinol (THC) and cannabidiol (CBD) is via smoking or vapor inhalation. Preclinical vapor models have been developed, although the vaporization devices and delivery methods vary widely across laboratories. This review examines the emerging field of preclinical vapor models with a focus on cannabinoid exposure in order to 1) summarize vapor exposure parameters and other methodological details across studies; 2) discuss the pharmacological and behavioral effects produced by exposure to vaporized cannabinoids; and 3) compare behavioral effects of cannabinoid vapor administration with those of other routes of administration. This review will serve as a guide for past and current vapor delivery methods in animals, synergize findings across studies, and propose future directions for this area of research.

Keywords

Cannabis; Preclinical Models; Vaping; Cannabinoids; THC; Vapor Exposure

Introduction

Cannabis is one of the most widely used drugs in the world, and in many areas, there is a growing trend towards its legalization for medical and recreational use. There is now an expansive retail market of cannabis and hemp products in the US and other countries (e.g., Canada, Australia) and use of these products continues to rise. In the most recent National Survey on Drug Use and Health, 8.4 million adults in the United States reported daily or almost daily use of cannabis, and 3.9 million met criteria for Cannabis Use Disorder in the past 12 months (SAMHSA, 2019). Rates of cannabis use among teens and adolescents is also high and rising: in 2019, prevalence of 12th graders' past 30-day use and past year use of cannabis was 6.4% and 38.5%, respectively (Johnston et al., 2019). Cannabis and related compounds have been proposed for medical use to treat neuropathic

*Corresponding author: Elise M. Weerts, Johns Hopkins Bayview Medical Campus, Behavioral Biology Research Center, 5510 Nathan Shock Drive, Suite 3000, Baltimore, MD 21224, USA. eweerts@jhmi.edu, Find us on Twitter: @EliseWeertsPhD, @CassieMoorePhD.

Conflicts of Interest:
There are no conflicts of interest.

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pain, tension, post-stroke neuroprotection, multiple sclerosis, epilepsy, cancer, PTSD, and other disorders (Greydanus et al., 2013). Despite the potential for medical benefit, there are significant harms associated with cannabis use, including psychiatric symptoms, abuse liability, cognitive effects, as well as risks from chronic smoking/vaping (Memedovich et al., 2018). At the same time cannabis use is increasing, societal acceptance of use is on the rise and perceptions of harm associated with cannabis use have decreased (Johnston et al., 2019).

Inhalation is the primary route of administration for cannabis and cannabinoid products (Jones et al., 2016; Lee et al., 2016; Trivers et al., 2019). Most commonly, cannabis is consumed by smoking (i.e., burning plant material), though coincident with the rise of e-cigarettes and other vaping devices, cannabis, −9-tetrahydrocannabinol (THC, the primary psychoactive constituent of cannabis), and other cannabinoid constituents are increasingly being vaped via these devices (Giroud et al., 2015; Ramo et al., 2015; Budney et al., 2015; Morean et al., 2015; Varlet et al., 2016). Recent estimated rates of vaping cannabis are reported to be between 20%−37% (past 30-days) and 60% (lifetime) in cannabis users in the US (Lee et al., 2016; Goodman et al., 2020; Schauer et al., 2020). In 2019, a national survey of US adolescents found that 14% of high-school seniors reported vaping cannabis in the past 30-days, a 2.5% jump from 2017 (Miech et al., 2019).

Vape devices, also termed “electronic nicotine delivery systems” (ENDS), were initially developed as a nicotine replacement product to reduce smoking and exposure to toxins inhaled via traditional combustible tobacco cigarettes (i.e., harm reduction), and promote smoking cessation. There are different types and generations of ENDS marketed under different names (e.g., electronic cigarettes, e-pipes, vaporizers, vape pens, hookah pens, etc.). ENDS typically consist of a battery, an electrical heater, and a reservoir for liquid, and can vary in appearance and configurations. The liquid (“e-liquid”) contains different concentrations of nicotine mixed with propylene glycol and/or vegetable glycerin, flavoring, and sometimes includes other additives such as ethyl alcohol, stabilizers, and non-nicotine pharmacologically active compounds. The different components of the e-liquid were developed to deliver specific vapor characteristics that emulate tobacco smoking (e.g., throat hit and vapor cloud as well as taste cues similar to or different from that of traditional tobacco flavors). Modified ENDS are available for the vaporization of dry herb, cannabis wax (butane honey oil concentrate), or a cannabis e-liquid, which is a mix of cannabis wax and propylene glycol and glycerol (Giroud et al., 2015). Some of these novel formulations, such as concentrated vape products (dabs, waxes), can contain up to 75% THC (Raber et al., 2015). Cannabinoid vaping cartridges are also available in a variety of formulations with purported concentrations of cannabinoids and constituent ratios of isolated cannabinoids (e.g., 10:1 CBD: THC), or so-called “full-spectrum” (i.e., containing phytocannabinoids) products.

The unique harms of vaping (e.g., higher potency, risk of contaminants) or potential benefits (e.g., reduced exposure to combustible materials in smoke) of vaping cannabis are not yet known and warrant further study. Accordingly, research initiatives have begun to examine the effects of inhaled cannabis using translational animal models. The use of these strategies is in the early stages; therefore, this review paper is meant to serve as a guide to what has so

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far been learned and how the field can systematize preclinical studies of vapor exposure for reliable and reproducible findings.

Preclinical drug vapor exposure systems

Laboratory animal models which allow precise control of drug history, parameters of drug exposure and dose, and environmental context are the first step in understanding cannabis and cannabinoid vapor effects under tightly controlled experimental conditions. Methods for e-cigarettes and other vaporization devices are increasingly being utilized in laboratory settings to study cannabinoids.

The earliest preclinical vapor chamber systems were developed for animal models of alcohol dependence and addiction (Rogers et al., 1979), and validated for use in pharmacological and behavioral studies (Gilpin et al., 2008; Gilpin et al., 2009; Mouton et al., 2016). Subsequently, vapor chamber systems were developed for use with freebase nicotine (Waldum et al., 1996). Bubbling of air with a constant air flow through a reservoir containing a nicotine solution causes evaporation and highly concentrated nicotine vapors are then passed through a drop-catch bottle and further diluted with clean air in an Erlenmeyer vacuum flask. The nicotine–air mixture is then distributed to vacuum sealed housing chambers. The concentrations of nicotine vapor can be adjusted by varying the flow rate at which nicotine is bubbled (Waldum et al., 1996; George et al., 2010).

Other methods have since been developed for vapor exposure via nebulizer or metered dose inhaler (MDI) systems for deilvery of aerosolized cannabinoids (Lichtman et al., 2000; Wilson et al., 2002) or opioids (Jaffe et al., 1989). Both nebulizers and MDI systems use air through an aqueous solution to create a mist of particles that can be inhaled. Initial studies using a nebulizer system delivered nose-only aerosolized cannabinoids to mice (Lichtman et al., 2000). The MDI system employs a modified, inverted separation funnel in a fume hood that draws air through glass wool and charcoal traps to deliver aerosolized THC (Wilson et al., 2002). Each MDI actuation contains an estimated fixed dose of THC, and blood and brain THC concentration increases in a dose dependent manner (Wilson et al., 2002). These systems were effective at producing behavioral and pharmacological effects of THC, with some limitations, such as effects of restraint and the use of solvents not approved for use in humans (Lichtman et al., 2000; Wilson et al., 2002). Around the same time, cannabis smoke exposure methods were being adapted from protocols developed in the 1970s (Fried and Nieman, 1973; Weinberg et al., 1977a; Weinberg et al., 1977b), which assess the effects of exposure to burned combustible cannabis plant material (Lichtman et al., 2001). In these procedures, smoke is drawn through tubing to via a vaccuum pump and systematically dispensed with a solenoid puffing device to the animal (Lichtman et al., 2001). Smoke exposure systems capture the chemical changes induced by heating of drug and e-liquid that may exert adverse health effects and/or behavioral effects on top of those produced by the drug constituents. Exposure to cannabis smoke produces behavioral effects and plasma levels of THC (Lichtman et al., 2001; Varvel et al., 2005; Varvel et al., 2006).

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Vape devices used in preclinical settings

There are multiple types of vape devices which employ a heating element to aerosolize drug for inhalation. For example, desktop vaporizors developed for human use (e.g., Volcano Vaporizer system, Storz & Bickel, Tuttlingen, Germany; VapirRise, Vapir Inc., Santa Clara, CA) were adapted for preclinical research (Manwell et al., 2014a; Hlozek et al., 2017; Brutman et al., 2019; Farra et al., 2020). These desktop vaporizors contain a temperature control system, convection heating, and a balloon bag system. Plant material or a pad saturated with ethanolic THC (ethanol then allowed to evaporate) is placed in the filling chamber and heated to produce vapor which is then collected into a detachable, disposable, plastic ballon. The ballon is fitted with a release valve, so that the collected vapor can be expelled into a sealed rodent cage to expose animals to the vapor for preset durations (Hazekamp et al., 2006; Manwell et al., 2014b). This technique produces dose-dependent plasma concentrations of THC in rats (Manwell et al., 2014b; Brutman et al., 2019).

The most common vape devices used in preclinical research are box mod ENDS, which consist of a vape tank, a coil (heating element, often referred to as the atomizer), and a battery-operated e-vape controller. The e-vape controller allows adjustment of equipment settings (V, W, temperature), while the type of coil determines the resistance (Ω). Commercially available preclinical vapor chamber systems integrate ENDS with sealed air-tight animal chambers (e.g., La Jolla Alcohol Research Inc., La Jolla, CA). Exposure chambers are typically the size of standard rodent housing cages (22–26L) though smaller custom chambers are also used (7–22L). The ENDS is connected via tubing to each animal cage and the controller can be triggered using standard software to activate the box mod to deliver puffs of vapor. The animal cage is fitted with an exit valve connected to a vacuum pump system which continuously pulls air out to circulate air, ensuring that drug vapor is delivered into the cage and cleared at a constant rate. As a relatively new technology, ENDS are constantly changing in attempts to improve drug delivery efficiency. Thus, laboratories adjust their exposure parameters based on the generation of vaporizer available for use in their studies. However, most studies to date have not included this information which decreases the rigor and reproducibility of study findings and complicates comparisons of data collected in different laboratories. For consistency across laboratories and across evolving technology, it is imperative that research publications include details about the equipment (e.g., chamber size, air flow rate) and settings used (watts, volts, resistance, temperature).

At the time of this review, studies using the box mod ENDS refer to either ‘first’ or ‘second’ generation mods, which describe the type of vaporizer (i.e., tank and coil) used in the vapor system. The Protank 3 Atomizer (Shenzhen Kanger Technology Co., LTD; Fuyong Town, Shenzhen, China) with MT32 coil operating at 2.2Ω is the most common first generation mod used for preclinical research (Nguyen et al., 2016; Nguyen et al., 2018; Javadi-Paydar et al., 2018; Nguyen et al., 2019a; Javadi-Paydar et al., 2019b; Freels et al., 2020). Later studies used second generation ENDS systems, which include sub-ohm tanks, such as the SMOK Tank Baby Beast TFV8 with an 0.2Ω M2 atomizer (SMOKTech, Nanshan, Shenzhen, China) or Herakles Sub Ohm Tank e-cigarette cartridges (Sense; Shenzhen Sense Technology Co., LTD; Baoan Dist, Shenzhen, Guangdong, China) (Nguyen et al., 2018;

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Nguyen et al., 2019b; Nguyen et al., 2019a; Freels et al., 2020). Second generation ENDS are more efficient, so in order to match the vapor delivered from 1st generation systems, 2nd generation protocols typically utilized a lower frequency and/or duration of puffs to deliver the same volume of drug vapor. For the purposes of this review, we will discuss vapor exposure parameters from ENDS in terms of the drug concentration in the e-vape tank and duration of exposure (e.g., 100 mg/ml, 30-min exposure). In Table 2, we include additional exposure parameters important for drug delivery, including the air flow rate, tank generation (where applicable), number of puffs, duration of each puff, and inter-puff interval (e.g., “4 × 10s every 5 min”). Further, to facilitate cross study comparisons, we will describe the time course of behavioral effects as time from vapor initiation.

Cage-type vapor exposure systems are more widely used than other technologies and have some methodological advantages. Specifically, rodents do not require restraint, are freely-moving throughout the chamber, and exposure can be to an idividual animal or a group of animals. Further, vapor exposure requires no surgery or injection, methods which can cause mild to moderate pain or distress. There are also multiple challenges specific to vapor exposure model. First, vapor is delivered to the whole chamber system and thus requires more drug than typical injection methods of drug administration. Second, vapor delivery volume per puff differs depending on the type/generation of the vape device used as well as puff duration. Third, since vapor exposure is to the whole animal in the cage-type vapor systems, drug may be delivered via mucous membranes (eyes, nose, etc.) and skin, as well the pulmonary tract. Fourth, parameters such as size of the chamber, drug particle size, air flow rate, and duration of exposure to drug vapor likely all contribute to efficacy and total drug delivered and maximum plasma concentration reached. Fifth, exposure to vapor or smoke itself might be stressful for an experimental animal, although systematic studies to verify if this is the case have not yet been done. Finally, respiration rates influence plasma drug concentration resulting in a degree of individual variability (i.e., titration of exposure by animal control over respiration). Many of these concerns highlight the imperative for published studies to include detailed methods of vapor delivery for interpretation of results, reproducibility of research, and cross comparisons across research studies, and to continue to perform validation studies on effects of vapor exposure.

Cannabinoid pharmacology

The *Cannabis sativa* plant contains over 100 isolated products that have been identified as cannabinoids (ElSohly et al., 2017; Lafaye et al., 2017). The effects of THC and other cannabinoids are mediated via actions on the endocannabinoid system. The endocannabinoid system is comprised of two major receptor types, cannabinoid type 1 (CB1R) and cannabinoid type 2 receptors (CB2R), their naturally occurring endogenous ligands 2-arachidonoylglycerol (2-AG) and arachindonoylethanolamide (anandamide) and enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (Ashton, 2001; for review, see Di Marzo et al., 2004; Bridgeman and Abazia, 2017). CB1R and CB2R belong to the superfamily of G-protein-coupled receptors.

THC selectively binds to CB1R and CB2R where it acts as a partial agonist. The psychoactive and dependence producing effects of THC are mediated primarily via CB1R

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effects and are blocked by the CBIR antagonist, SR141716 (rimonabant) (for review see Pertwee, 2006; Cooper and Haney, 2008). CB1R activation by THC and other agonists also modulates the endocannabinoids AEA and AN, causing retrograde activation of glutamatergic and GABAergic neurons throughout the brain and having indirect effects on the mesolimbic dopamine system (Ng Cheong Ton et al., 1988; Chen et al., 1990; Pistis et al., 2002; Castillo et al., 2012; Bloomfield et al., 2019). There is strong clinical evidence that cannabis and THC can produce euphoria, increase heart rate, impair neurocognitive function and motor skills, and induce feelings of paranoia and anxiety (Lichtman et al., 2002; D'Souza et al., 2004; Haney, 2005; Spindle et al., 2018). With chronic use, cannabis produces dependence in a subset of users and incidence of anxiety and mood disorders (depression, PTSD and schizophrenia) is more common in individuals who use cannabis regularly (Lichtman et al., 2002; D'Souza et al., 2004; Haney, 2005; Leweke and Koethe, 2008; Ashton and Moore, 2011; Spindle et al., 2018). While there is strong evidence of cannabis and THC abuse liability, there is also evidence of therapeutic benefits for specific conditions due to the analgesic, appetite stimulant and anti-emetic properties of cannabinoids. Synthetic formulations of THC (e.g., dronabinol, marinol) are FDA-approved to treat or prevent nausea and vomiting in cancer patients (Fraguas-Sanchez and Torres-Suarez, 2018), and to increase appetite and reduce weight loss in people with wasting disease associated with AIDS (Haney et al., 2005; Badowski and Perez, 2016).

Cannabidiol (CBD) is a major phytocannabinoid that does not cause the same "high" or "mood altering" effects associated with THC (Devinsky et al., 2014). In contrast to THC, CBD has a complex pharmacological profile, with diverse actions at many receptors. It has very low binding affinity for CB1R receptors, but may act via negative allosteric modulation of CB1R as well as activity at CB2R (Pertwee, 2012). Other CBD signaling mechanisms include serotonin-1A (5-HT$_{1A}$), mu and delta opioid receptors, and transient receptor potential V1 (TRPV1) and V2 (TRPV2), GPR55, GPR18 from the TRP superfamily of nonselective, ligand-gated cation channels, and other transient receptor potential channels (Kathmann et al., 2006; McPartland et al., 2015; Russo and Marcu, 2017). The effects of CBD are not THC-like, and CBD has a low abuse liability profile (Babalonis et al., 2017; Viudez-Martinez et al., 2018; Spindle et al., 2020). CBD has demonstrated efficacy as an anti-convulsant and a pharmaceutical grade CBD formulation (Epidiolex®) derived from *Cannabis sativa* is approved by the US Food and Drug Administration for seizures associated with Lennox-Gastaut syndrome and Dravet syndrome (Food and Drug Administration, 2018; Szaflarski et al., 2018; Franco and Perucca, 2019).

"Synthetic Cannabinoid" is a general term that describes a diverse group of compounds synthesized to act on the CB1 and CB2 cannabinoid receptors to produce similar effects to THC (Castaneto et al., 2014). Synthetic cannabinoids were developed as research tools to investigate effects of CB1 and CB2 activation, but have since emerged as popular drugs of abuse ("K2" or "spice") that are typically smoked (Vandrey et al., 2012). The majority of synthetic cannabinoids bind to CB1 receptors with greater affinity than THC, resulting in intense psychoactive effects, as well as a high incidence of adverse events such as psychosis and acute neurological effects (Tait et al., 2016). As the focus of the present review is cannabis and cannabis constituents, we direct interested readers to the following reviews for

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more information on the topic of synthetic cannabinoids (Spaderna et al., 2013; Castaneto et al., 2014; Martinotti et al., 2017).

Cannabinoid pharmacokinetics

Cannabinoid pharmacokinetics are dynamic, and bioavailability of cannabinoids depends on a multitude of factors including route of administration, dose, frequency of use, among others (for review, see Huestis, 2007). The majority of pharmacokinetic studies have so far focused on THC and CBD. While many clinical studies also measure THC's primary active and inactive metabolites, 11-hydroxy- ^{9}-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- 9-tetrahydrocannabinol (THC-COOH), these have not yet been widely explored in preclinical studies. Therefore, for the purposes of this review, we will summarize briefly the pharmacokinetics of THC and CBD, with a focus on the differences between the routes of administration observed in preclinical and clinical studies.

Preclinical vapor exposure studies of cannabinoid pharmacokinetics demonstrate that THC vapor exposure generates physiologically relevant concentrations of THC in blood and brain (summarized in Table 1), with comparable pharmacokinetics to humans after inhaling cannabis. In humans, inhalation of smoked or vaporized cannabis is characterized by fast absorption through the lungs resulting in almost immediate detectable drug levels (CBD and THC) in plasma (Ohlsson et al., 1986; Huestis et al., 1992), which peak after 5–10 minutes, decreasing to near nondetectable levels (<5 ng/ml) within 3 hours (Huestis et al., 1992; Schwope et al., 2011). Similarly, in rats, vapor exposure to THC or CBD results in peak plasma concentrations (C_{max}) occurring rapidly following administration in a concentration-dependent manner (Javadi-Paydar et al., 2018; Javadi-Paydar et al., 2019a). For example, rats exposed to 200 mg/ml vaporized THC for 30-min have a C_{max} of 140–180 ng/ml THC immediately after the end of the exposure session (T_{max}: 5 min), with THC levels decreasing to <10 ng/ml after 2–3 hours post-session (Nguyen et al., 2016; Javadi-Paydar et al., 2018). A comparable THC C_{max} is observed 30-min after an intraperitoneal (i.p.) injection of 10 mg/kg THC (Nguyen et al., 2016), or in humans 5–10 min after smoking a marijuana cigarette containing ~34 mg THC (Hartman et al. 2015; Huestis et al. 1992). Rats exposed to 100 mg/ml vaporized CBD for 30 min had C_{max} of ~185 ng/ml immediately after the end of the exposure session (T_{max}: 5 min), with CBD levels decreasing to ~30 ng/ml after 2 hours post-session (Javadi-Paydar et al., 2019a). These CBD levels were within the range produced by 10–30 mg/kg, i.p. CBD (Javadi-Paydar et al., 2019a). Similar pharmacokinetics of CBD were observed in two human laboratory studies, where after vaping (100 mg/mL for 11-min) or smoking (~14 mg) CBD, plasma concentrations were approximately 65 ng/mL after 10–15 min and <5 ng/mL after 1–2 hr (Arkell et al., 2019; Kintz, 2020).

Vapor exposure/inhalation of THC and CBD results in higher plasma concentrations and faster absorption compared to oral administration, where oral THC and CBD undergo considerable first pass hepatic metabolism and slow and erratic absorption (Wall et al., 1983; Grotenhermen, 2003; Newmeyer et al., 2017; Taylor et al., 2018). The pharmacokinetic parameters of oral consumption of THC and CBD are also affected by the formulation (solution vs. capsule) and food (high fat food vs. fasted state). Studies in humans and animals have observed low (6–20%) oral bioavailability of THC and CBD, peak

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concentrations occurring typically between 1–5 hrs, and marked inter-individual variation (Ohlsson et al., 1980; Law et al., 1984; Samara et al., 1988; Consroe et al., 1991; Goodwin et al., 2006; Lile et al., 2013; Hlozek et al., 2017; Newmeyer et al., 2017). Rats consuming THC in gelatin (average 2–3 mg/kg) had THC blood levels between 2–4 ng/ml after 1-hr (Kruse et al., 2019), mirroring human studies of oral THC (10–50 mg) producing low (<10 mg/ml) plasma THC concentrations (Nadulski et al., 2005; Goodwin et al., 2006; Newmeyer et al., 2017). A preclinical study of pharmacokinetics of a high dose of THC or CBD (10 mg/kg) in sesame oil administered by oral gavage produced peak serum concentrations of ~165 and ~275 ng/ml, respectively, at 1 and 2-hr post-administration (Hlozek et al., 2017). Similarly, one study administering high oral doses of THC (90 mg) to regular cannabis users observed an average C_{max} of ~50 ng/ml (range: 9.0– 127.1) and T_{max} ranging from 1–12h (median: 3.3h) (Lile et al., 2013). C_{max} after oral CBD (900 mg) was ~80 ng/ml (range: 1.6 to 271.9 ng/ml) while T_{max} was observed at 180 min (range: 120 to 360 min) in a human laboratory study (Haney et al., 2016).

Compared to vapor exposure/inhalation, i.v. administration of THC and CBD produces lower peak serum concentrations that occur later (Hlozek et al., 2017): in rats, i.p. or subcutaneous (s.c.) injection causes serum levels to peak at 30 or 60 min post-injection, respectively (Hlozek et al., 2017; Britch et al., 2017). Though cannabis and cannabinoids are not typically administered i.v., human pharmacokinetic studies have employed this technique, determining that i.v. administration of THC or CBD produces peak concentrations after 10-min, with C_{max} of 82 ±87.4 and 119.2 ±166.5 ng/ml for intravenous (i.v.) doses of 2.5 and 5.0 mg, respectively (D'Souza et al., 2004).

Pharmacokinetic interactions of THC and CBD

THC and CBD may have functional pharmacokinetic and behavioral interactions (for review, see Boggs et al., 2018; Freeman et al., 2019). Both preclinical and clinical evidence suggest that CBD inhibits THC metabolism, likely through actions on CYP450 enzymes that metabolize both drugs (Qian et al., 2019). In rats, co-administration of CBD+THC produced higher serum/brain levels of THC compared to THC alone, observed after oral and s.c. routes (Klein et al., 2011; Hlozek et al., 2017). Similarly, in human laboratory studies, smoking and vaping cannabis containing THC+CBD produced higher levels of plasma THC compared to smoking cannabis with THC alone (van de Donk et al., 2019; Arkell et al., 2019). However, multiple human studies using oral or i.v. administration have found no effects of CBD on plasma THC and THC metabolite levels in blood (Nadulski et al., 2005; Bhattacharyya et al., 2010; Karschner et al., 2011). The discrepancies in these studies may reflect differences in route of administration or doses used, or differences in dose inhaled by the subject (e.g., self-titration). More research is needed to understand the functional interactions of CBD and THC on pharmacokinetics and behavioral effects of cannabis and cannabinoids.

Behavioral effects of Cannabinoids

To date, the majority of experiments on cannabinoids in animals have primarily utilized injection (i.p., i.v., or s.c.) routes of administration, with relatively few laboratories utilizing

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vapor exposure models. As such studies are in early stages, most research has focused on THC only and demonstration of vapor effects using standard behavioral paradigms for cannabinoids (e.g., the behavioral tetrad). Preclinical studies that employ inhalation/ exposure methods are summarized below and in Table 2. Of note, this is not meant to be an exhaustive review of all known behavioral effects of cannabinoids but is focused on the behaviors that have been studied thus far in cannabinoid vapor exposure models. There is evolving literature on sex differences in responses to cannabis and cannabinoids. In the current review, sex differences will only be discussed in the context of results from vapor exposure studies presented here; therefore, we wish to direct interested readers to the following excellent review articles that fully address sex differences in cannabinoid effects (Crane et al., 2013; Craft et al., 2013; Cooper and Craft, 2018).

Cannabinoid Tetrad Assay

Cannabis, and THC specifically, induces a classical 'tetrad' of behavioral effects in rats and mice, which includes hypothermia, hypolocomotion, catalepsy, and antinociception (Martin et al., 1991; Metna-Laurent et al., 2017). The 'behavioral tetrad' is often used as an in vivo bioassay of effects of THC and other CB1 agonists (Pertwee, 2006). These four behaviors are readily antagonized by co-administration with the selective CB1 receptor antagonist SR141716 and are absent in mice lacking the CB1 receptor (Ledent et al., 1999; Pertwee, 2006).

Hypothermia—THC causes hypothermia in rodents (Smirnov and Kiyatkin, 2008) and nonhuman primates (McMahon et al., 2005; Taffe, 2012) via CB1 activation (Metna-Laurent et al., 2017). Injections of THC (i.p.) dose-dependently reduce body temperatures at doses from 0.5–200 mg, with maximum decreases of as much as 6°C (Smirnov and Kiyatkin, 2008; Paronis et al., 2012). THC-induced hypothermia can last >7 hours, with peak effects occurring 2–4 hours after injection (Paronis et al., 2012; Taffe et al., 2015). Hypothermic effects of i.p. THC are similar in males and females (Wiley et al., 2007). THC vapor exposure also reduces body temperature in rats (Nguyen et al., 2016; Javadi-Paydar et al., 2018; Nguyen et al., 2019a). At the highest concentrations tested (100–200 mg/mL; 30–40 minutes exposure), temperatures decreased roughly 2–3° C, which is comparable to hypothermic effects seen after an i.p. injection of 20 mg/kg of THC (Nguyen et al., 2016; Javadi-Paydar et al., 2018). In male and female rats, peak hypothermic effects occur at 30–60 minutes post-vapor initiation and are back to control levels after 4 hours (Nguyen et al., 2018; Javadi-Paydar et al., 2018; Nguyen et al., 2019a). Tolerance to the hypothermic response to THC vapor emerges after chronic dosing (2–3x daily sessions for >4 days), with evidence that tolerance occurs more quickly in female rats (Nguyen et al., 2018). In female rats, the hypothermic effects of THC exposure did not differ across phases of the estrous cycle (Javadi-Paydar et al., 2018). Thus, while both THC administered i.p. and via vapor exposure produce hypothermia in rats, THC vapor exposure produces a quicker, more transient drop in body temperature compared to i.p. injection of THC.

When administered via i.p. injection, CBD (20–200 mg/kg) has not be shown to have effects on body temperature (El-Alfy et al., 2010; Taffe et al., 2015). However, exposure to 400 mg/ml CBD vapor for 30 minutes caused hypothermia in rats with peak effects occurring

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60–90 minutes after vapor initiation (Javadi-Paydar et al., 2018). The hypothermic effects of CBD were less than those produced by THC vapor (Javadi-Paydar et al., 2018). CBD-induced hypothermia may be mediated in part via serotonergic mechanisms as CBD effects on body temperature were partially blocked by pre-treatment with the 5-HT_{1A} receptor WAY 100,635 (Taffe et al., 2015). This discrepancy in effects between injected and vapor CBD suggests that route of administration is crucial for determining effects of CBD.

CBD has been shown to modulate the hypothermic effects of THC when co-administered, however these results have been mixed. For example, when injected at a 1:1 CBD:THC ratio (10 mg/kg, i.p.), the hypothermic effects of THC were attenuated compared to THC alone (Todd and Arnold, 2016; Todd et al., 2017), while a higher dose (30 mg/kg, i.p.) at this 1:1 ratio potentiated the hypothermic effects of THC alone (Taffe et al., 2015). At higher CBD:THC ratios (4:1, 10:1, 50:1; i.p.), an additive effect of CBD on THC-induced hypothermia was observed (Hayakawa et al., 2008). One study has looked at hypothermic effects of THC and CBD vapor co-exposure (Javadi-Paydar et al., 2018). When administered in a 4:1 ratio at threshold concentrations (100 mg/ml CBD, 25 mg/ml THC), the hypothermic effects of THC were exacerbated. However, when administered in a 1:2 ratio (100 mg/ml CBD, 200 mg/ml THC), there were comparable effects of CBD+THC and THC vapor alone on reducing body temperature (Javadi-Paydar et al., 2018). Therefore, most research points to CBD increasing the magnitude of THC-induced hypothermic effects, though there may be some attenuation at lower CBD:THC ratios at certain doses, which may also depend on the route of administration.

Hypolocomotion—THC is generally acknowledged to reduce spontaneous locomotor activity at moderate to high doses (20–40 mg/kg, i.p.) in mice and rats (Martin et al., 1991; Smirnov and Kiyatkin, 2008; El-Alfy et al., 2010; Taffe et al., 2015). These hypolocomotor effects of i.p. THC last up to 4-hrs after administration (McMahon and Koek, 2007; Taffe et al., 2015). However, a biphasic dose effect of THC on locomotor activity has also been observed in multiple studies, where low doses of THC (0.1–2.0 mg/kg, i.p.) produce hyperlocomotion (Sanudo-Pena et al., 2000; El-Alfy et al., 2010; Polissidis et al., 2010; Katsidoni et al., 2013). Interestingly, doses of THC that produce hyperlocomotion align with doses that produce rewarding effects (Braida et al., 2004; Katsidoni et al., 2013). Both hyper- and hypolocomotion are reversed by CB1 antagonists (Jarbe et al., 2002; Katsidoni et al., 2013). Repeated dosing of THC has also been shown to induce "rebound hyperactivity," where following the acute hypolocomotion observed on day 1, chronic 1x daily THC (10 mg/kg, i.p.) caused increased locomotor activity on subsequent days, with tolerance to this effect occurring after 12 days (Todd et al., 2017).

Oral administration of THC (10 mg/kg) produced hypolocomotion after 120–150 min (Hlozek et al., 2017). Oral consumption of a lower dose of THC (~2.5 mg/kg) in gelatin produced an initial increase in locomotion (first 5 min), which returned to control levels for the duration of the 60-min test period (Kruse et al., 2019). Studies of THC vapor exposure (12.5–100 mg/mL) have also found initial increases of locomotor activity (30–60 min post-vapor initiation), with locomotor suppression occurring 2–4h after vapor exposure (Nguyen et al., 2019a; Javadi-Paydar et al., 2019b). Higher concentrations of THC vapor exposure (25–200 mg/mL) show overall reduced locomotor activity in a concentration dependent

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manner (Nguyen et al., 2016; Javadi-Paydar et al., 2018). In sum, THC vapor exposure produces both increases and decreases in locomotor activity, as is observed after injected or oral THC; more research is needed to assess route differences on locomotor effects at equivalent doses.

Catalepsy—Catalepsy, or immobilization, is another classical test of the cannabinoid tetrad, and is observed after administration of THC and CB1 agonists in rats and mice (Sanudo-Pena et al., 2000; McMahon and Koek, 2007). Catalepsy is the inability of an animal to correct an experimentally-imposed posture: most commonly tested through placement of the experimental subject's forepaws on a bar or ring and measuring the length of time the animal remains immobile (Sanberg et al., 1988). THC causes catalepsy at moderate to high doses of THC (2.5–100 mg/kg, i.p.) in rats and mice (Sanudo-Pena et al., 2000; McMahon and Koek, 2007). Catalepsy occurs at THC doses (i.p.) 3- to 6-fold higher than doses where locomotor suppression is observed (McMahon and Koek, 2007; Wiley et al., 2007). THC smoke exposure (20–200 mg combustible plant material, 3.46% THC) caused catalepsy in mice, with an estimated ED_{50} of 103 mg (95% CI: 63–170) (Lichtman et al., 2001). In this study, cannabis smoke exposure resulted in plasma levels of THC comparable to those observed after 3–10 mg/kg i.p. THC (Lichtman et al., 2001). Aerosolized THC exposure with an MDI system also produced dose-dependent increases in catalepsy, with an ED_{50} of 30 mg THC (95% CI: 22–39) in mice (Wilson et al., 2002). To our knowledge, there have not yet been any reported studies on catalepsy following THC vapor exposure.

Antinociception—THC, CB1 agonists, and other cannabinoids cause antinociception, or reduced transmission of painful stimuli to the CNS (Pertwee, 2001; Craft et al., 2012; Britch et al., 2017). The antinociceptive effects of THC are blocked by CB1R, but not CB2R, antagonists (Booker et al., 2009). Acute THC (10–176 mg/kg, i.p.) produces dose-dependent antinociception with peak effects occurring 60–90 minutes post-injection (Wiley et al., 2007; El-Alfy et al., 2010; Metna-Laurent et al., 2017; Craft et al., 2019). A study of male and female rats indicates similar efficacy of THC on antinociception in both sexes, where acute THC ED_{50} values for antinociception were 6 mg/kg, i.p. (CI 3–13) and 12 mg/kg, i.p. (CI 7–19) for female and male rats, respectively (Wiley et al., 2007). Antinociceptive effects of i.p. THC have been observed up to 240 min (Nguyen et al., 2016). Following repeated dosing with THC (10 mg/kg, i.p., 2x daily for 10 days), rats show substantial tolerance to the antinociceptive effects of THC (Wiley et al., 2007).

Experiments using THC vapor exposure (200 mg/ml) showed exposure-dependent nociceptive effects, where longer durations of exposure (20 and 30-min), but not shorter (10-min) resulted in longer tail-withdrawal latencies, observed from 30–120 minutes post-exposure and returning to control levels after 3 hrs (Nguyen et al., 2016). These nociceptive effects were blocked with pretreatment with the CB1 antagonist SR141716 (Nguyen et al., 2016). A separate study using a lower THC concentration (100 mg/ml, 30-min exposure) also observed nociception 60-min after vapor initiation (Javadi-Paydar et al., 2018). Repeated THC vapor exposure (3x daily sessions; 200 mg/ml, 30-min exposure) caused tolerance to the antinociceptive effects of THC (Nguyen et al., 2018). Overall,

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similar antinociceptive effects of i.p. THC and THC vapor exposure have been observed, with differences in respect to time course.

Anxiety-like behavior

Cannabis and THC have biphasic effects on anxiety; acute administration of low doses of THC (less than 1 mg/kg) produces an anxiolytic effect, while higher doses (>1 mg/kg) are anxiogenic (Viveros et al., 2005; Patel and Hillard, 2006). In mice, THC (0.3 mg/kg, i.p.) increased time spent in the light compartment of a light-dark box, a measure of anxiolytic behavior (Berrendero and Maldonado, 2002; Harte-Hargrove and Dow-Edwards, 2012). Acute THC (1–5 mg/kg, i.p.) increased anxiety-like behavior in a social interaction test in rats (Malone et al., 2009; Klein et al., 2011; Manwell et al., 2019). Acute THC (2–5 mg/kg, i.p.) also shows anxiogenic effects in the elevated plus maze and open field 'emergence' test (Manwell et al., 2019). In adolescent rats, chronic administration (7d) of a low-dose of THC (2 mg/kg, i.p.) increased, while a high dose (15 mg/kg, i.p.) decreased, time spent in the center of an open field arena, representing an anxiolytic and anxiogenic response respectively (Harte-Hargrove and Dow-Edwards, 2012). The anxiogenic effects of the high dose of THC were driven primarily by responses in female rats (Harte-Hargrove and Dow-Edwards, 2012). Furthermore, discontinuation of chronic THC produced anxiety-like behaviors, which were greater in female than male rats (Harte-Hargrove and Dow-Edwards, 2012). CBD modulates the effects of THC on anxiety-like behavior: administration of CBD:THC given at a 1:1 ratio exacerbates the anxiogenic effects of THC alone (Klein et al., 2011), while high CBD:THC ratios (e.g., 20:1) may block the anxiogenic effects (Malone et al., 2009).

Effects of THC on anxiety-like behavior are CB1 receptor-mediated, as SR141716 blocks the anxiolytic and anxiogenic effect of THC (Berrendero and Maldonado, 2002). SR141716 precipitates anxiety-like behavior in THC or cannabis withdrawn animals and has also shown anxiogenic effects in naïve animals (Navarro et al., 1997; Lichtman et al., 1998; Wilson et al., 2006). A high dose of vaporized cannabis (450 mg/3 mice, 15-min exposure) produced an anxiogenic response in mice tested in the open field test (Farra et al., 2020). Mice exposed to cannabis smoke (~3.46–6.93 mg THC) for 5 days and then treated with SR141716 showed precipitated withdrawal similar to the levels observed in mice that had been chronically treated with 5–10 mg/kg, i.p. THC (Wilson et al., 2006).

Feeding/appetite

Food intake is increased by THC, CB1 agonists, and other cannabinoids due to increases in appetite, palatability, and/or the reinforcing properties of food (Berry and Mechoulam, 2002; Jager and Witkamp, 2014). The neuropharmacological mechanisms of cannabinoid effects on feeding include interactions with hypothalamic and extrahypothalamic systems, including orexigenic and anorexigenic hormones (leptin, neuropeptide-Y) and classic neurotransmitter systems (dopamine, GABA) (Di Marzo et al., 2001; Berry and Mechoulam, 2002; De Luca et al., 2012; Jager and Witkamp, 2014; Williams et al., 2015; Koch et al., 2015).

THC and other CB1 agonists, including the endocannabinoids 2-AG and AEA, induce hyperphagia while CB1 antagonists such as SR141716 suppress appetite and reduce feeding

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behavior (Williams et al., 1998; Rowland et al., 2001; Koch, 2001; McLaughlin et al., 2003; Higgs et al., 2005). In a standard preclinical test of hyperphagia, animals are sated prior to drug administration, and following a pretreatment period, food is given and subsequent food intake is measured. In sated animals, THC at low doses (0.1–1 mg/kg, i.p.; 0.5–3 mg/kg, p.o.) induces hyperphagia of plain chow and palatable food (e.g., high sugar) (Williams et al., 1998; Koch, 2001; Higgs et al., 2005; Farrimond et al., 2010). Hyperphagic effects dissipate after the first testing hour (Farrimond et al., 2010). After initial hyperphagia, rats compensate by reducing intake, normalizing calories consumed in a 24-h period to that of control animals (Koch, 2001). Higher doses of THC (2.5 mg/kg, i.p.;   3 mg/kg, p.o.) do not produce hyperphagia, likely due to nonspecific behavioral impairment (Williams et al., 1998; Koch, 2001). Rats exposed to THC vapor (10 mg) showed increased food intake of a plain chow diet in the first hour of a 4-hr test (Manwell et al., 2014b). In a separate study, rats exposed to cannabis vapor exposure (~62.4 mg THC) also showed increased plain chow intake measured after 2-hrs, while 200 and 400 mg cannabis (~15.6 and 31.2 mg THC, respectively) did not affect total 2-hr intake (Brutman et al., 2019). Exposing rats to cannabis vapor (~62.4 mg THC) also increased cumulative intake of a high-sugar, palatable food from 120–180 min relative to air-exposed controls (Brutman et al., 2019).

THC and CB1 agonists increase palatability of nutrient-dense, palatable food (i.e., high in fats and/or sugar). While hyperphagia is increased generally, one experiment observed a greater magnitude of hyperphagia of a palatable food compared to plain chow after THC administration (0.5–1 mg/kg, i.p.)(Koch, 2001). THC (0.5–1 mg/kg, i.p.) increased hedonic taste reactivity to a sweet solution, measured using validated facial reactions (Jarrett et al., 2005; De Luca et al., 2012). Increased taste reactivity to sucrose in the THC condition was associated with facilitation of dopamine release in the nucleus accumbens shell compared to vehicle + sucrose (De Luca et al., 2012).

Cannabinoids modulate motivation for food, measured by responding under progressive ratio (PR) schedules of reinforcement, where subjects must exhibit a greater number of behavioral responses within a particular session to obtain food reinforcement. In this paradigm, the “break point,” where each animal stops working for the reinforcement within a session, is used as a measure of motivation (Solinas and Goldberg, 2005). THC has a biphasic effect on break points for food reinforcement, with increases at lower doses (1–3 mg/kg, i.p.). and decreases at higher doses (>5 mg/kg, i.p.) of THC (Solinas and Goldberg, 2005; Higgs et al., 2005). A study using a mathematical model of PR responding for sucrose reinforcement did not find an effect of THC (0.3–3 mg/kg, i.p.) on breakpoint, but found an increase in incentive value of sucrose (α) (Olarte-Sanchez et al., 2015). High doses of CB1 agonists and THC can cause non-specific behavioral disruption, often resulting in lower observable food intake that is confounded by motor impairment, reduced locomotion, etc. (Schulze et al., 1988; Drews et al., 2005).

In seeming contrast to THC effects on food intake, chronic THC administration causes reductions in body weight in rats (Nelson et al., 2019) and analogously rates of obesity are lower in cannabis users (Smit and Crespo, 2001; Hayatbakhsh et al., 2010). The mechanism of cannabis and cannabinoids on energy expenditure, metabolism, and body weight are

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not yet well understood and are an active area of research (Pagotto et al., 2006; Ignatowska-Jankowska et al., 2011; Ruiz de Azua et al., 2017).

Learning and Memory

Acute cannabis and THC administration have largely been shown to induce cognitive impairments in humans and laboratory animals (Ranganathan and D'Souza, 2006; Crane et al., 2013; Broyd et al., 2016). Acute THC has been shown to cause deficits in reversal learning and working memory tasks in rodents and nonhuman primates (Fadda et al., 2004; Wright et al., 2013). To date, there are no studies that have investigated effects of vaporized THC or cannabinoids on learning and memory effects. There are several studies that have examined effects of cannabis smoke exposure on different cognitive tasks (Schulze et al., 1989; Niyuhire et al., 2007; Blaes et al., 2019). The first study administered cannabis cigarette smoke to rhesus monkeys via a face mask, finding that 1 and 5 puffs of cannabis smoke impaired performance accuracy in a delayed match to sample task, particularly at longer delay periods (Schulze et al., 1989). In a study using mice trained to complete a Morris water maze task, the effects of cannabis smoke exposure or i.p. THC 30-min on either acquisition of or retrieval was investigated (Niyuhire et al., 2007). Both cannabis smoke exposure (50–200 mg) and i.p. THC (1–10 mg/kg) impaired acquisition (memory encoding) and retrieval (short term memory), while pretreatment with a CB1 antagonist blocked these deleterious effects of cannabis smoke/i.p. THC (Niyuhire et al., 2007). In contrast, a recent study utilizing a delayed response working memory task in adult male and female rats found that while i.p. THC (3 mg.kg) impaired performance in both male and female rats, cannabis smoke (from 1, 3, or 5 cigarettes (700 mg each) containing 5.6% THC administered to 4 cages at a time) either had no effect (males) or enhanced working memory performance (females) (Blaes et al., 2019). While plasma concentrations of THC weren't measured in this study, a study by the same group reported 10 ng/ml THC after exposure to smoke from 5 cannabis cigarettes, indicating a low dose of THC administered via the cannabis smoke (Ravula et al., 2018). Thus, it may be that low doses of THC, particularly when inhaled, may have discrepant, and sex-dependent, effects on learning and memory than effects observed after injection.

Reward/reinforcement

Studies in humans have demonstrated that the rewarding and positive reinforcing effects of cannabis are due to THC, which exerts its effects via the endocannabinoid system (Cooper and Haney, 2008). Animal studies have found both rewarding and aversive effects of THC and synthetic cannabinoids, depending on the paradigms and parameters used to study these effects (detailed below).

Conditioned effects—Conditioned place preference (CPP) tests the conditioned rewarding (or aversive) effects of an administered substance. In this paradigm, rats or mice are exposed to a drug and then confined to one compartment of a two-compartment chamber. On alternate trials, animals receive exposure to the vehicle (e.g., saline) prior to confinement in the alternate compartment. On the final test day, animals are allowed to move freely between compartments, and an increase or decrease in time spent on the drug-paired side of the chamber is indicative of conditioned rewarding or aversive effects, respectively.

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In tests of the conditioned effects of THC, low doses (0.075–0.75 mg/kg, i.p.) produce preference, while higher doses (5–6 mg/kg, i.p.) produce aversion (Braida et al., 2004). The aversion seen at higher doses reflects a dysphoric effect of THC and CB1 agonists, which may be overcoming any rewarding effects of the drug (Parker and Gillies, 1995; McGregor et al., 1996). If a primer dose of THC is given prior to CPP conditioning (i.e., pre-exposure), it can shift preference for THC-paired compartments (Valjent and Maldonado, 2000), supporting a theory of an initial dysphoric effect of THC upon first administration, particularly with injection routes of administration. Pretreatment with CBD prior to THC conditioning (1:1, 10 mg/kg) also can reverse the CPA seen with THC-alone (Klein et al., 2011). The rewarding effects of THC are blocked if co-administered with a CB1 antagonist (Braida et al., 2004).

A study of the conditioned rewarding effects of THC vapor in rats found that 10-min THC vapor exposure (10 mg; delivered in 16L air over 10-min) prior to conditioning sessions produced a preference for the THC-vapor paired side (Manwell et al., 2014a). Alternatively, rats exposed to the same dose, but over a longer period (10 mg; delivered in 16L air over 20-min) did not show a preference for the THC-paired side (Manwell et al., 2014a). An alternate procedure, which used the same duration and dose, but reduced the volume (10 mg; delivered in 8L air over 10-min) exposed to two rats simultaneously, also did not produce preference, potentially due to an aversive concentration of vapor or less total dose exposure (10 mg/2 rats vs. 10 mg/1 rat) (Manwell et al., 2014a). The differential effects seen in these experiments highlight the importance of parameters on dose received, and subsequently behaviors observed, in vapor exposure models. A representative blood concentration of THC in rats exposed to THC (10 mg; delivered in 8L air over 5-min) were 400 and 300 ng/ml/kg at 20 and 40 minutes post-exposure, respectively (N=1) (Manwell et al., 2014a). These THC blood concentrations were comparable to an injection of 1.5 mg/kg THC (350 and 410 ng/ml/kg at 20 and 40 minutes post-injection, respectively), which produced aversion in the CPP test, highlighting the importance of route of administration on the conditioned rewarding effects of THC (Manwell et al., 2014a).

Operant self-administration—Drug self-administration is the ‘gold standard’ paradigm in animal models to demonstrate drug reinforcement and abuse liability. Drug reinforcement, as with any reinforcement, refers to the process by which drug presentation, contingent upon a behavioral response, increases the likelihood of that behavioral response (Young and Herling, 1986). Typically, animals are trained to emit a behavior (e.g., nose-poke), which is followed by drug delivery. Reinforcement is demonstrated if the behavioral response associated with drug delivery is maintained, and if drug-associated responding exceeds responding for the drug vehicle. Prior rodent studies have primarily used simple schedules of reinforcement and short duration of daily drug access (e.g., 1-hr sessions) (Tanda and Goldberg, 2003; Panlilio et al., 2010).

Self-administration of THC, using the i.v. route, has been difficult to demonstrate using these standard procedures. Although rats self-administered the aminoalkylindole cannabinoid agonist WIN 55,212–2, substitution of THC did not maintain responding (Lefever et al., 2014). In contrast, selective high affinity CB1R agonists, which have greater potency than THC, were self-administered in a dose-dependent manner (Martellotta et al.,

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1998; Fattore et al., 2001; Deiana et al., 2007; Fattore et al., 2007). Studies in rats have demonstrated THC self-administration, particularly under conditions known to enhance drug reinforcement (e.g., food and water deprivation) (Cooper and Haney, 2009). The strongest demonstration of the reinforcing effects of THC is from studies in squirrel monkeys (Tanda et al., 2000; Justinova et al., 2003). In these studies, researchers modified several key aspects of the procedure that most likely to contributed to its success over prior attempts, including use of very low THC doses (2–4 μg/kg/injection), rapid drug delivery, exposure to full range of doses, and frequent vehicle substitution early in training to increase sensitivity and discrimination of doses (for review, see Panlilio et al., 2010). The authors determined that these changes in procedural parameters were critical to establish THC self-injection.

The importance of using low THC doses is further supported by place conditioning studies, as discussed above. THC conditions place preference primarily at low doses (e.g., 0.075–0.75 mg/kg). Higher doses (1.5–15) mg/kg do not produce place preference and can produce conditioned aversion (Murray and Bevins, 2010). Thus, it seems likely that vaporization of THC, which results in increased bioavailability and allows for rapid delivery, and careful manipulation of access parameters, may provide optimal conditions to facilitate THC reinforcement and the necessary contingent associations that develop with operant tasks.

Recently, the first instance of cannabis vapor self-administration in rats was demonstrated (Freels et al., 2020). This study evaluated the reinforcing effects of vaporized cannabis extracts rich in THC or CBD using operant self-administration procedures. Under FR4 and PR schedules of reinforcement, rats had greater responding for vapor deliveries of a THC-rich cannabis compared to CBD-rich cannabis and a propylene glycol/vegetable glycerin vehicle vapor. Rats showed discrimination (>2:1 active vs. inactive nose-poke responding) for both THC- and CBD- rich cannabis extract vapor, but not for vehicle vapor. Rats administered a greater amount of vapor deliveries early in the session, consistent with the loading dose phenomenon seen in drug self-administration models (Pickens et al., 1978). Motivation to obtain THC-rich cannabis extract vapor was higher than vehicle or CBD-rich cannabis extract vapor, as evidenced by higher breakpoints under the PR schedule. The reinforcing efficacy of THC-rich cannabis extract was CB1R mediated, as pretreatment with the CB1R antagonist AM251 reduced responding. Further, the authors showed that response-contingent delivery of vaporized cannabis extracts produced behavioral and physiological changes that were consistent with passive vapor models; namely, reduced locomotor activity, increased daily food intake, and plasma THC and CBD levels that were consistent with amount of vapor deliveries obtained (Freels et al., 2020).

Conclusions and Future Directions

Vapor exposure models have good face validity for translational research into cannabis and cannabinoids, as inhalation (smoking, vaping, dabbing) are the primary routes of administration for people using cannabinoids recreationally or medicinally. Route of administration is important from a translational approach and for interpretation of cannabinoid pharmacology and toxicology. So far, cannabinoid vapor exposure models have shown that blood levels of THC are present and comparable to humans or other routes of administration in animals that produce behavioral effects. Physiology and behavior

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observed after vapor exposure has so far closely matched what is observed when THC is administered by other routes of administration, including the classic cannabinoid tetrad. The use of vaporization (and oral) routes of administration better informs the pharmacokinetic/pharmacodynamic profile of these compounds as they are used in humans. Next steps for the field of preclinical cannabinoid research include 1) expanded use of vapor exposure routes of administration, 2) use of vapor self-administration models to evaluate reinforcing effects of cannabinoids, 3) investigations into other cannabis constituents (e.g., terpenoids and cannabinoids other than THC) via oral and vapor exposure routes.

In general, experiments should include multiple routes of cannabinoid administration used by humans (oral, vapor, transdermal) when possible. As vapor exposure methods are increasingly being validated, it is important to compare effects with those produced by injection and/or oral routes of administration for approximate dose response curve comparisons. Furthermore, establishing parameters in vapor exposure needs to be done systematically to increase reproducibility between labs. With vapor exposure models, drug administration actually refers to a group of parameters that are used during the exposure protocol (e.g., drug concentration in the e-vape tank, puff frequency and duration, inter-puff-interval, and length of vapor exposure time). The term “dose” should largely be avoided in the context of vapor exposure models, and drug amounts instead expressed as a concentration (weight/volume). Further, reporting of all details of the vapor exposure protocol is necessary to provide a framework for understanding approximate drug exposure amounts.

As research on cannabinoids extends to vapor models, it is clear both passive exposure to vapor (i.e., experimenter administered), and operant self-administration methods will play a role. Operant self-administration procedures can provide information on drug reinforcement, abuse liability, incentive salience, and shifts in motivational behavior involved in drug taking. Passive models will be important for generating key information on dose-response relationships, drug tolerance and physical dependence. Ultimately, vapor models will allow for the evaluation of a broader range of cannabinoid products, and permit explorations of potential of new pharmacotherapeutics. Expansion of the use of preclinical vapor exposure models has great promise for advancing cannabinoid research and allowing science to catch up to the already widespread public use of and interest in cannabis.

Funding Sources:

This work was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number R21DA046154 and the Johns Hopkins University Dalio Fund in Decision Making and the Neuroscience of Motivated Behaviors.

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Table 1.

Blood THC concentrations after various vapor exposure methods. THC Dose refers to either total drug vaporized (in mg) per session (MDI, Smoke exposure system, Volcano-type vape) or concentration of drug (in mg/ml) in the reservoir/e-vape tank (Nebulizer, ENDS). Sampling time is calculated from exposure initiation. Data are presented as Mean ±SEM. Mean ±SEM values in *italics* represent data extracted from published figures using DataThief III software (Tummers, 2006).

Species/Sex	Drug	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Sampling time	Plasma Conc. (ng/ml)	Route Comparison: THC Dose, Route	Sampling time	Plasma Conc. (ng/ml)	Ref.
Nebulizer										
Adult ICR Mice (M)	THC	7.5 L/min air flow	10 min	10 mg/ml	30 min	133 ±36	*N.A.*	*N.A.*	*N.A.*	(Lichtman et al., 2000)
Metered-Dose Inhaler (MDI)										
Adult ICR Mice (M)	THC	1 actuation every 5s; 60 ml/min air flow	10 min	~18 mg per 4 mice	30-min	409 ±86	1 mg/kg, i.v.	20-min	102 ±6	(Wilson et al., 2002)
				~36 mg per 4 mice	30-min	788 ±273	3 mg/kg, i.v.	20-min	365 ±39	
				~54 mg per 4 mice	30-min	1132 ±240	10 mg/kg, i.v.	20-min	1324 ±38	
Smoke exposure system: Combustible plant material										
Adult ICR Mice (M)	Cannabis plant material (3.46% THC)	1 × 8s puff every 16s; 400 ml/min air flow	2–4 min	~1.7 mg	30-min	149 ±43	1 mg/kg, i.v.	20-min	69 ±7	(Lichtman et al., 2001)
				~3.5 mg	30-min	254 ±34	3 mg/kg, i.v.	20-min	226 ±21	
				~6.9 mg	30-min	402 ±77	10 mg/kg, i.v.	20-min	720 ±20	
Adult ICR Mice (M)	Cannabis plant material (3.46% THC)	1 × 8s puff every 16s; 360 ml/min air flow	up to 5 min	~1.7 mg	25-min	98 ±13	0.3 mg/kg, i.v.	20-min	33 ±2	(Wilson et al., 2006)
				~3.5 mg	25-min	241 ±36	1 mg/kg, i.v.	20-min	102 ±7	
				~6.9 mg	25-min	385 ±110	3 mg/kg, i.v.	20-min	323 ±36	
							5 mg/kg, i.v.	20-min	522 ±56	
							10 mg/kg, i.v.	20-min	1325 ±190	
				~6.9 mg	25-min	365 ±31	3 mg/kg, i.v.	20-min	365 ±39	
					45-min	255 ±43		40-min	255 ±29	
					1-hr	281 ±52		1-hr	186 ±7	
					2-hr	221 ±64		2-hr	56 ±6	
					3-hr	78 ±11		3-hr	26 ±3	
					4-hr	96 ±30		4-hr	14 ±1	

Species/Sex	Drug	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Sampling time	Plasma Conc. (ng/ml)	Route Comparison: THC Dose, Route	Sampling time	Plasma Conc. (ng/ml)	Ref.
Adult ICR Mice (M)	Cannabis plant material (5.19% THC)	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	~2.6 mg per 6 mice	20-min	85 ±12				(Varvel et al., 2005)
				~10.4 mg per 6 mice	20-min	475 ±74				
	THC added to placebo plant material	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	5 mg per 6 mice	20-min	61 ±6	0.3 mg/kg, i.v.	20-min	22 ±3	
				20 mg per 6 mice	20-min	300 ±38	1 mg/kg, i.v.	20-min	100 ±10	
							3 mg/kg, i.v.	20-min	325 ±38	
	Cannabis extract (33.5% THC) added to placebo plant material	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	5 mg per 6 mice	20-min	74 ±9	0.3 mg/kg, i.v.	20-min	19 ±3	
				20 mg per 6 mice	20-min	286 ±35	1 mg/kg, i.v.	20-min	101 ±24	
							3 mg/kg, i.v.	20-min	325 ±39	
Adult ICR Mice (M)	Cannabis plant material (5.19% THC)	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	~10.4 mg	20-min	*404 ±43*	0.3 mg/kg, i.v.	20-min	*58 ±14*	(Varvel et al., 2006)
							3 mg/kg, i.v.	20-min	*480 ±72*	
Adult Wistar rats (M)	Cannabis plant material (5.7% THC)	1 × 2s puff every 1 min; air flow rate *N.S.*	1 hr; daily for 12 days	5 cannabis cigarettes	1-hr	224.9 ±3.1	*N.A.*	*N.A.*	*N.A.*	(Bruijnzeel et al., 2016)
Adult Wistar rats (M)	Cannabis plant material (5.3% THC)	1 × 2s puffs every 1 min; air flow rate *N.S.*	50 min	5 cannabis cigarettes per 4 rats	C_{max}	18.2	*N.A.*	*N.A.*	*N.A.*	(Ravula et al., 2019)
			100 min	10 cannabis cigarettes per 4 rats	C_{max}	29.6				
Volcano-type vaporizer										
Adult Sprague-Dawley rat (M) N=1	THC	balloon filled to 8L; No air flow	5 min	1 mg	30-min	157.5 †	0.25 mg/kg, i.p.	20-min	151.37 †	*(Manwell et al., 2014)*
					50-min	155.67 †		40-min	173.17 †	
				5 mg	30-min	223.06 †	0.5 mg/kg, i.p.	20-min	210.54 †	
					50-min	209.38 †		40-min	244.47 †	
				10 mg	30-min	402.31 †	1.0 mg/kg, i.p.	20-min	244.46 †	

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Species/Sex	Drug	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Sampling time	Plasma Conc. (ng/ml)	Route Comparison: THC Dose, Route	Sampling time	Plasma Conc. (ng/ml)	Ref.
					50-min	301.06†		40-min	395.33†	
							1.5 mg/kg, i.p.	20-min	349.33†	
								40-min	410.89†	
Adult Wistar rats (M)	THC	45s of vaporization; No air flow	5 min	20 mg per 4 rats	5-min	*295±52*	10 mg/kg, s.c.	30-min	*10 ±4*	(Hlozek et al., 2017)
					20-min	*106±24*		1-hr	*21 ±12*	
					35-min	*69±47*		2-hr	*18 ±13*	
					1-hr	*58±23*		4-hr	*16 ±9*	
					2-hr	*46±23*		8-hr	*7 ±2*	
					4-hr	*36±22*		24-hr	*5 ±2*	
					8-hr	*16±8*	10 mg/kg, p.o.	30-min	*96 ±51*	
					24-hr	*5±1*		1-hr	*167 ±88*	
								2-hr	*143 ±51*	
								4-hr	*72 ±56*	
								8-hr	*13 ±9*	
								24-hr	*13 ±4*	
Adult Long-Evans rats (M)	Cannabis plant material (7.8% THC)	Vaporizer parameters *N.S.;* 1 L/min air flow	10-min	~62.4 mg	20-min	35.54 ± 9.51	*N.A.*	*N.A.*	*N.A.*	(Brutman et al., 2019)
					40-min	28.94 ± 5.02				
					70-min	21.80 ± 2.75				
Adult C57BL/6 mice (M)	Cannabis plant material (10.3% THC)	1 × 10s puff every 20 sec; 2 L/min air flow	15-min	5.2 mg per 3 mice	15-min	*9 ±2*	*N.A.*	*N.A.*	*N.A.*	(Farra et al., 2020)
				10.3 mg per 3 mice	15-min	*25 ±8*				
				15.5 mg per 3 mice	15-min	*49 ±12*				
				30.9 mg per 3 mice	15-min	*82 ±12*				
				~46.4 mg per 3 mice	15-min	*136 ±5*				

Species/Sex	Drug	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Sampling time	Plasma Conc. (ng/ml)	Route Comparison: THC Dose, Route	Sampling time	Plasma Conc. (ng/ml)	Ref.
Electronic Nicotine Delivery System (ENDS)										
Adult Sprague-Dawley rats (M)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	200 mg/ml	30-min	*175 ±22*	0.3 mg/kg	30-min	*5 ±2*	(Nguyen et al., 2016)
					60-min	*50 ±9*	3 mg/kg	30-min	*50 ±6*	
					90-min	*25 ±4*	10 mg/kg	30-min	*162 ±46*	
					120-min	*17 ±5*				
					180-min	*9 ±4*				
	Cannabis extract	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	40 min	~116 mg/mL	40-min	*68 ±7*				
					60-min	*24 ±6*				
					90-min	*10 ±5*				
					120-min	*4 ±3*				
					180-min	*4 ±2*				
Adult Wistar rats (M/F)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	25 mg/ml	35-min	*7 ±1 (F)* *8 ±2 (M)*	*N.A.*	*N.A.*	*N.A.*	(Javadi-Paydar et al., 2018)
					1-hr	*9 ±1 (F)* *4 ±1 (M)*				
				100 mg/ml	35-min	*43 ±6 (F)* *40 ±9 (M)*				
					1-hr	*15 ±2 (F)* *18 ±5 (M)*				
					2 hr	*4 ±1 (F&M)*				
					4 hr	*3 ±1 (F&M)*				
				200 mg/ml	35 min	*138 ±22 (F)* *138 ±41 (M)*				
					1 hr	*50 ±8 (F)* *61 ±19 (M)*				

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Species/Sex	Drug	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Sampling time	Plasma Conc. (ng/ml)	Route Comparison: THC Dose, Route	Sampling time	Plasma Conc. (ng/ml)	Ref.
Adult Wistar rats (M/F)	THC	1 × 6s puff every 5 min; (2nd gen); 2–3 L/min air flow	30 min	200 mg/ml	35 min	303 ±37.4 (F) 362 ±52.5 (M)	*N.A.*	*N.A.*	*N.A.*	(Nguyen et al., 2018)
Adult Wistar rats (M)	THC	Puff parameters *N.S.*; 1 L/min air flow	30 min	100 mg/ml	35-min	*67 ±8*	10 mg/kg, i.p.	35-min	*65 ±13*	(Nguyen et al., 2019b)
					1-hr	*30 ±6*		1-hr	*48 ±4*	
					2-hr	*21 ±2*		2-hr	*23 ±3*	
					4-hr	*4 ±1*		4-hr	*17 ±4*	
Adult Wistar rats (M/F)	THC	4 × 10s puffs every 5 min; (2nd gen); 1 L/min air flow	30 min; (acute)	100 mg/ml	35-min	*99 ±6 (F) 86 ±7 (M)*	*N.A.*	*N.A.*	*N.A.*	(Nguyen et al., 2019a)
		4 × 10s puffs every 5 min; (2nd gen); 1 L/min air flow	30 min; daily for 4d (chronic)	100 mg/ml	35-min	*141 ±19 (F) 170 ±17 (M)*				
		4 × 10s puffs every 5 min; (2nd gen); 1 L/min air flow	30 min	50 mg/ml	35-min	*89 ±11 (F) 26 ±6 (M)*				
				100 mg/ml	35-min	*148 ±23 (F) 109 ±17 (M)*				
				200 mg/ml	35-min	*165 ±13 (F) 141 ±22 (M)*				

(M) = Males, (F) = Females; N.S. = Not Stated; N.A. = Not applicable;

† denotes ng/ml/kg.

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Table 2.

Behavioral outcomes in cannabinoid vapor exposure models. THC Dose refers to either total drug vaporized (in mg) per session (MDI, Smoke exposure system, Volcano-type vape) or concentration of drug (in mg/ml) in the reservoir/e-vape tank (Nebulizer, ENDS). Outcomes are described as differences from vehicle vapor. An indication of "concentration-dependent" signifies differences between THC exposure conditions. Time course (minutes from vapor initiation) of observed behavioral effects are noted in parentheses, where post-hoc test indicates $p<0.05$ from vehicle group at same time point.

Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
Nebulizer								
Adult ICR Mice (M)	THC	7.5 L/min air flow	1–10 min	0.01–10 mg/ml	**Nociception**, i.e. tail withdrawal latency, was measured 30-min after exposure to THC vapor.	↓ nociception after 10 mg/ml THC vapor exposure for 10-min. Lower concentrations (0.01, 0.1, 1.0) or shorter durations of exposure (1 or 3 min). had no effect. These effects were blocked by pre-treatment with the CB1 antagonist SR141716, but pretreatment with the opioid antagonist naloxone had no effect.	*N.A.*	(Lichtman et al., 2000)
		7.5 L/min air flow	10 min	10 mg/ml	**Nociception**, i.e. tail withdrawal latency, was measured 15, 30, 50, and 70-min after exposure to THC vapor.	↓ nociception after exposure to THC vapor (15–40 min).	*N.A.*	
					Locomotor activity was measured in activity chambers for 40-min after exposure to THC vapor.	— no effects of THC vapor exposure on locomotor activity.	*N.A.*	
					Body temperature was measured with a rectal thermometer 15, 30, 50, and 70-min after exposure to THC vapor.	— no effects of THC vapor exposure on body temperature.	*N.A.*	
Metered Dose Inhaler (MDI)								
Adult ICR Mice (M)	THC	1 actuation every 5s; 60 ml/min air flow	10 min	~18–54 mg THC per 4 mice; (~0.9 mg THC/ actuation)	**Locomotor activity** was measured in activity chambers for 5-min, 15-min after exposure to THC aerosol.	↓ locomotor activity after 40 or 60 actuations (~36 and 54 mg THC).	*N.A.*	(Wilson et al., 2002)
					Nociception, i.e. tail withdrawal latency, was measured 30-min after exposure to THC aerosol.	↓ nociception after 40 or 60 actuations (~36 and 54 mg THC).	*N.A.*	

Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					Catalepsy was measured using the ring test procedure 50-min after exposure to THC aerosol.	↑ catalepsy after 40 or 60 actuations (~36 and 54 mg THC).	*N.A.*	
					Body temperature was measured with a rectal thermometer 70-min after exposure to THC aerosol.	↓ body temperature after 40 or 60 actuations (~36 and 54 mg THC).	*N.A.*	
Smoke exposure system: combustible plant material								
Adult ICR Mice (M)	Cannabis plant material (3.46% THC)	1 × 8s puff every 16s; 400 ml/min air flow	2–4 min	~1.7–10.4 mg THC (50–300 mg cannabis)	**Locomotor activity** was measured in activity chambers for 5-min, 15-min after exposure to cannabis smoke.	— exposure to both cannabis smoke and placebo smoke reduced locomotor activity, suggesting a confounding effect of the restraint used and/or smoke exposure.	*N.A.*	(Lichtman et al., 2001)
					Nociception, i.e. tail withdrawal latency, was measured 30-min after exposure to cannabis smoke.	↓ nociception after exposure to cannabis smoke (~3.5, 6.9, and 10.4 mg THC).	*N.A.*	
					Catalepsy was measured using the ring test procedure 50-min after exposure to cannabis smoke.	↑ catalepsy after exposure to cannabis smoke (~3.5, 6.9, and 10.4 mg THC).	*N.A.*	
					Body temperature was measured with a rectal thermometer 70-min after exposure to cannabis smoke.	— exposure to both cannabis smoke and placebo smoke reduced body temperature, suggesting a confounding effect of the restraint used and/or smoke exposure.	*N.A.*	
Adult ICR Mice (M)	Cannabis plant material (5.19% THC)	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	~0.5–10.4 mg THC (10–200 mg cannabis)	**Locomotor activity** was measured in activity chambers for 5-min, 15-min after exposure to cannabis smoke.	— exposure to both cannabis smoke and placebo smoke reduced locomotor activity, suggesting a confounding effect of the restraint used and/or smoke exposure.	*N.A.*	(Varvel et al., 2005)
					Nociception, i.e. tail withdrawal latency, was measured 30-min after exposure to cannabis smoke.	↓ nociception after exposure to cannabis smoke (~10.4 mg THC). Pretreatment with the CB1 antagonist SR141716 blocked this effect.	*N.A.*	
					Catalepsy was measured using the ring test procedure 50-min after exposure to cannabis smoke.	↑ catalepsy after exposure to cannabis smoke (~10.4 mg THC). Pretreatment with the CB1 antagonist SR141716 blocked this effect.	*N.A.*	

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					Body temperature was measured with a rectal thermometer 70-min after exposure to cannabis smoke.	↓ body temperature after exposure to cannabis smoke (~5.2 and 10.4 mg THC). Pretreatment with the CB1 antagonist SR141716 blocked this effect.	*N.A.*	
Adult ICR Mice (M)	Cannabis plant material (5.19% THC) + CBD	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	~0.65–10.4 mg THC (12.5–200 mg cannabis) + 3–30 mg CBD	**Nociception**, i.e. tail withdrawal latency, was measured 30-min after exposure to cannabis smoke with varying amounts of added CBD	↓ nociception after exposure to cannabis smoke (~10.4 mg THC), which was not modified by addition of CBD.	THC (0.1–3 mg/kg, i.v.) ↓ nociception, which was not modified by pretreatment with 3 mg/kg CBD, i.v.	(Varvel et al., 2006)
	Placebo cannabis plant material + THC/ CBD	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	1–10 mg THC + 30 mg CBD	**Nociception**, i.e. tail withdrawal latency, was measured 30-min after exposure to placebo cannabis smoke (ethanol extracted) with varying amounts of added THC + CBD	↓ nociception after exposure to placebo cannabis smoke with added THC (3–10 mg THC); THC effects were not modified by addition of CBD.		
Adult ICR Mice (M)	Cannabis plant material (3.46% THC)	1 × 8s puff every 16s; 360 ml/min air flow	up to 5 min	~1.73–6.92 mg THC (50–200 mg cannabis)	**Precipitated withdrawal behaviors** (paw tremors, head shakes, scratching) were assessed by injecting 10 mg/kg SR141716 (CB1R antagonist) into rats who had 5-days exposure to cannabis smoke.	↑ SR141716 increased paw tremors in rats with a history of exposure to cannabis smoke (~3.46 and 6.92 mg THC, but not 1.73 mg THC). SR141716 -induced withdrawal was dependent on number of exposures to cannabis smoke.	SR141716 dose-dependently increased paw tremors in rats with a history of THC injections (3 and 10 mg/kg, i.p.)	(Wilson et al., 2006)
Adult ICR Mice (M)	Cannabis plant material (5.19% THC)	1 × 8s puff every 16s; 1 L/min air flow	1–2 min	~2.6–10.4 mg THC (50–200 mg cannabis)	**Working memory testing** was performed using a modified Morris Water Maze to test cannabis smoke effects on acquisition or retrieval.	↓ acquisition and retrieval of search strategies in the Morris water maze were disrupted after pre-exposure to smoke from 50, 100, and 200 mg cannabis. These effects were blocked with pretreatment of SR141716 (3 mg/kg, i.p.).	i.p. THC ↓ impaired acquisition (3 and 10 mg/kg) and retrieval (10 mg/ kg). These effects were blocked with pretreatment of SR141716 (3 mg/kg, i.p.).	(Niyuhire et al., 2007)
Adult Wistar rats (M)	Cannabis plant material (5.7% THC)	1 × 2s puff every 1 min; air flow rate *N.S.*	1 hr	5 cannabis cigarettes	**Locomotor activity** was measured in an open field arena for 30-min, 15-min following cannabis smoke exposure, in rats who received chronic exposure (8–9 days) to cannabis smoke.	↓ locomotor activity after cannabis smoke exposure from 15–30 min of an open field test.	*N.A.*	(Bruijnzeel et al., 2016)

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					Precipitated withdrawal behaviors were assessed by injecting 5 mg/kg SR141716 into rats who received chronic exposure (12–15 days) to cannabis smoke.	↑ SR141716 increased somatic withdrawal signs in all rats, but to a greater extent in rats with a history of exposure to cannabis smoke.	*N.A.*	
					Anxiety-like behavior in the elevated plus maze was assessed in rats who received chronic exposure (7 weeks) to cannabis smoke.	__ no effect of cannabis smoke exposure history on % open arm time, a measure of anxiety-like behavior.	*N.A.*	
Adult Long Evans rats (M/F)	Cannabis plant material (5.6% THC)	1 × 2s puffs every 1 min; air flow rate *N.S.*	*N.S.*	1–5 cannabis cigarettes (~700 mg each)	**Working memory testing** was performed using a delayed response working memory task after exposure to acute cannabis smoke from 1, 3, or 5 cannabis cigarettes.	<u>Females:</u> ↑ working memory performance after exposure to smoke from 1, 3, and 5 cannabis cigarettes, but not placebo smoke. <u>Males:</u> __ no effect of cannabis smoke exposure on working memory performance (accuracy) *Female, but not male, rats show enhanced working memory performance after cannabis smoke exposure.	THC (3 mg/kg, *i.p.*) ↓ impaired working memory performance in both male and female rats.	(Blaes et al., 2019)
Adult Wistar rats (M)	Cannabis plant material (5.3% THC)	1 × 2s puffs every 1 min; air flow rate *N.S.*	50–100 min daily	5–10 cannabis cigarettes	**Brain stimulation reward thresholds** were measured using intracranial self-stimulation (ICSS) procedures in rats 60-min after cannabis smoke exposure, measured during chronic daily sessions for 2 weeks.	↓ brain stimulation reward thresholds in rats exposed to daily cannabis smoke (10 cigarettes; 100 min daily) compared to air-exposed controls on days 4, 6, 8.	*.N.A.*	(Ravula et al., 2019)
					SR141716 effects on brain stimulation reward thresholds were measured using ICSS procedures in rats who had daily exposure to cannabis smoke for 3 weeks. On the test day, SR141716 was injected 45-min after the smoke exposure session, 15-min prior to ICSS.	↑ brain stimulation reward thresholds by SR141716 (0.3–3 mg/kg, i.p.) in rats with chronic exposure to daily cannabis smoke.	*N.A.*	
Volcano-type vaporizer								
Adult Sprague-	THC	balloon filled to 8L; No air flow	5 min	2–20 mg per 2 rats	**Conditioned place preference (CPP) or**	__ no effects of THC (2, 10, or 20 mg) vapor exposure on CPP/CPA.	THC injected at 1.5 mg/kg	(Manwell et al., 2014a)

Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
Dawley rats (M)					**aversion (CPA)** was measured after 8 conditioning sessions with THC vapor (2, 10, 20 mg) and vehicle vapor exposure. Morphine (5 mg/kg, i.p.) and THC (1.5 mg/kg, i.p.) groups were run as comparisons.	Morphine produced CPP, while THC injected i.p. produced CPA.	produced conditioned place aversion, while vaporized THC produced neither CPP nor CPA.	
		balloon filled to 8 or 16L; No air flow	10–20 min	10 mg per 1–2 rats	**Conditioned place preference** was measured after 4 conditioning sessions with THC vapor (10 mg) or air exposure. Vapor exposure was systematically varied by length of exposure time or number of rats exposed.	↑ CPP in rats exposed to 10 mg THC vapor delivered across 10 min (4L delivered every 2.5 min to 1 rat). No CPP or CPA was observed in rats exposed to 10 mg THC vapor delivered across 20 min (4L delivered every 5 min to 1 rat) or in rats exposed to 10 mg THC across 10 min (2L delivered every 2.5 min to 2 rats).	*N.A.*	
Adult Sprague-Dawley rats (M)	THC	balloon filled to 8L; No air flow	5 min	10 mg per 2 rats	**Locomotor activity** was measured for 4h after exposure to THC vapor in 7 sessions across 15d.	↑ locomotor activity in the first hour of testing in each of 7 sessions across 15d; no differences between THC and air groups between hours 2–4.	*N.A.*	(Manwell et al., 2014b)
		balloon filled to 8L; No air flow	5 min; 7 total sessions	10 mg per 2 rats	**Cross-sensitization to morphine** (5 mg/kg, s.c.) was assessed using a locomotor activity test 4 days after chronic THC vapor exposure (7 sessions over 15d).	— no effects of prior THC exposure on cross-sensitization to morphine, i.e. no differences in locomotor activity in response to morphine in a THC-exposed vs. vehicle vapor-exposed group.	*N.A.*	
		balloon filled to 8L; No air flow	10 min	1–10 mg per 2 rats	**Food intake, water consumption, and locomotor activity** was measured over 4h after exposure to THC vapor.	↑ food intake in the first hour of exposure to 10 mg, but not 1 or 5 mg, THC vapor. — no effects of THC vapor exposure on water consumption. ↑ locomotor activity (60-min) and ↓ locomotor activity (120-min) after exposure to 10 mg, but not 1 or 5 mg, THC vapor.	THC (0.1, 0.3, 0.5, 1 mg/kg, i.p.) had no effect on food intake, water consumption, or locomotor activity	
Adult Sprague-Dawley rats (M)	THC	balloon filled to 8L; No air flow	5 min	1–10 mg per 2 rats	**Extinction of naloxone-precipitated morphine withdrawal-induced conditioned place aversion (CPA)** was assessed in rats after exposure to THC vapor prior to daily extinction	↑ extinction of CPA in rats exposed to THC vapor exposure (5 and 10 mg THC, but not 1 mg THC).	THC (1.0 mg/kg, i.p.) impaired extinction of naloxone CPA, while 0.5 and 1.5 mg/kg THC, i.p. had no effect on rate of extinction.	(Manwell and Mallet, 2015)

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					sessions over the course of 20 days			
Adult Wistar rats (M)	THC	45s of vaporization; No air flow	5 min	20 mg per 4 rats	**Locomotor activity** was measured in an open field arena for 30 min, immediately (5-min) after THC vapor exposure.	↓ locomotor activity overall after exposure to 20 mg THC vapor. Activity after THC exposure was higher in the first 5-min block, but lower for the duration of the test (5–30 min).	THC (10 mg/kg, p.o.) reduced locomotor activity to a greater extent than vapor exposure. THC (10 mg/kg, s.c.) had no effect on locomotor activity.	(Hlozek et al., 2017)
					Prepulse inhibition, or sensorimotor gating, was measured using the acoustic startle test immediately (5-min) after THC vapor exposure.	__ no effects of THC exposure on prepulse inhibition.	There were no effects of s.c. (10 mg/kg) or oral (10 mg/kg) THC on prepulse inhibition.	
Adult Long-Evans rats (M)	Cannabis plant material (7.8% THC)	Vaporizer parameters *N.S.*; 1 L/min air flow	10 min	~15.6 – 62.4 mg THC	**Plain chow intake** was measured over 2h after exposure to THC vapor in sated rats.	↑ total plain chow intake in two hours after exposure to 800 mg cannabis vapor (~62.4 mg THC), but not lower amounts of cannabis vapor (200 or 400 mg; ~15.6 or ~31.2 mg THC, respectively).	*N.A.*	(Brutman et al., 2019)
	Cannabis plant material (7.8% THC)	Vaporizer parameters *N.S.*; 1 L/min air flow	10 min	~62.4 mg THC	**Palatable food intake** was measured over 4h after exposure to THC vapor in sated rats.	↑ cumulative palatable food intake from 120–180 min after exposure to cannabis vapor (~62.4 mg THC) relative to air-exposed controls.		
Adult C57BL/6 mice (M)	Cannabis plant material (10.3% THC)	1 × 10s puff every 20 sec; 2 L/min air flow	15-min	~46.4 mg per 3 mice	**Anxiety-like behavior** was measured with the open field test.	↑ anxiety-like behavior was observed in male mice after exposure to cannabis vapor (~46.2 mg THC) relative to air exposed controls.	*N.A.*	(Farra et al., 2020)
Electronic Nicotine Delivery System (ENDS)								
Adult Sprague-Dawley rats (M)	THC	4 × 10s puffs every 5 min (1st gen); 1 L/min air flow	10–30 min	200 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after 10, 20, or 30-min exposure to THC vapor	↓ body temperature after 20 or 30-min, but not 10-min exposure to THC (30–120 min). __ no effects of THC exposure on locomotor activity.	Peak temperature decreases were ~ 1°C lower after 10 mg/kg i.p. THC. Differences observed with respect to time course.	(Nguyen et al., 2016)
Adult Wistar rats (M)	THC	4 × 10s puffs every 5 min (1st gen); 1 L/min air flow	30 min	50–100 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after	↓ body temperature after exposure to 50 mg/ml (120–180 min) and 100 mg/ml THC (60–240 min); concentration-dependent effect.	*N.A.*	

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					exposure to THC vapor of different concentrations	↓ locomotor activity after exposure to 100 mg/ml THC (120–240 min).		
Adult Wistar rats (F)	THC	4 × 10s puffs every 5 min (1st gen); 1 L/min air flow	30 min	25–50 mg/ml		↓ body temperature after exposure to 25 mg/ml (120–240 min) and 50 mg/ml THC (60–240 min); concentration-dependent effect. — no effects of THC exposure on locomotor activity.	*N.A.*	
Adult Sprague-Dawley rats (M)	Cannabis extract or THC	4 × 10s puffs every 5 min (1st gen); 1 L/min air flow	40 min	~116 mg/ml THC (crude extract) or 50 mg/ml THC	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after 10, 20, or 30-min exposure to cannabis extract vapor	↓ body temperature after exposure to 50 mg/ml THC (50–105 min) and crude cannabis extract (50–70 min); greater effects after THC alone. — no effects of THC exposure on locomotor activity.	*N.A.*	
Adult Wistar rats (M)	THC	4 × 10s puffs every 5 min (1st gen); 1 L/min air flow	10–30 min	200 mg/ml	**Nociception** was measured by tail withdrawal latency for 4h after 10, 20, or 30-min exposure to THC vapor	↓ nociception after 20 or 30-min, but not 10-min, exposure to THC (60 min).	THC vapor-induced antinociception (20–30 min conditions) was equivalent to 3–10 mg/kg i.p THC.	
Adult Wistar rats (M/F)	THC	4 × 10s puffs every 5 min (1st gen); 1 L/min air flow	40 min	12.5–100 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after exposure to THC vapor	Females: ↓ body temperature after exposure to 50 and 100 mg/ml THC; concentration-dependent effect. — no effects of THC exposure on locomotor activity. Males: ↓ body temperature after exposure to 50 and 100 mg/ml THC; concentration-dependent effect. ↓ locomotor activity after exposure to 50 and 100 mg/ml THC. *Males, but not females, showed hypolocomotion following exposure to THC vapor.	*N.A.*	(Javadi-Paydar et al., 2018)
Adult Wistar rats (F)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	40 min	25 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after exposure to THC vapor in estrus and diestrus phases of the estrous cycle	↓ body temperature after exposure to THC; similar effects in estrus and diestrus. — no effects of THC vapor exposure on locomotor activity.	*N.A.*	
			30 min	50 mg/ml		↓ body temperature after exposure to THC vapor (estrus: 60–180 min; diestrus 60–270 min). ↓ locomotor activity after exposure to THC vapor (estrus: 120–180; diestrus: 180–240).	*N.A.*	

Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
						Temperature and locomotor activity were slower to return to baseline levels in rats tested in diestrus.		
Adult Wistar rats (M/F)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	100 mg/ml	**Nociception**, i.e. tail withdrawal latency, was measured 60-min after exposure to THC vapor. Female rats were tested in estrus and diestrus phases of the estrous cycle	Females: ↓ nociception after exposure to THC, no differences in estrus and diestrus. Males: ↓ nociception after exposure to THC. *No differential effects of sex on the antinociceptive effects of THC vapor.	*N.A.*	
Adult Wistar rats (M/F)	CBD	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	10–40 min	100 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after 10, 20, or 40-min exposure to CBD vapor	Females: ↓ body temperature after 40-min exposure to CBD (60–90 min). ↓ locomotor activity after 10-min (60–90 min), 20-min (90-min) and 40-min exposure to CBD (90–240 min). Males: ↓ body temperature after 20 and 40-min (60–120 min) exposure to CBD. ↓ locomotor activity after 20-min (150-min) exposure to CBD. *CBD vapor exposure (20-min) reduced body temperature in male, but not female, rats while a longer exposure duration (40-min) reduced temperature in both sexes. Female rats showed hypolocomotion after all CBD exposure conditions (10, 20, and 40-min), while male rats showed hypolocomotion only after 20-min CBD exposure condition.	*N.A.*	
Adult Wistar rats (M)	THC, CBD, THC + CBD (2:1)	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	200 mg/ml THC; 100 mg/ml CBD	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after exposure to THC, CBD, or THC+CBD vapor	↓ body temperature after exposure to THC (60–180 min), CBD (60–120), and THC+CBD (60–180); THC and THC+CBD effects were greater than CBD alone. ↓ locomotor activity after exposure to THC, CBD (120-min), and THC+CBD (60–120 min). THC and THC+CBD effects were greater than CBD alone.	*N.A.*	
Adult Wistar rats (M/F)	THC, CBD, THC + CBD (1:4)	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	25 mg/ml THC; 100 mg/ml CBD	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after	Females: ↓ body temperature after exposure to THC (30–240 min), CBD (30–60 min), and THC+CBD (120–210 min) vapor.	*N.A.*	

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					exposure to THC, CBD, or THC+CBD vapor	↓ locomotor activity after exposure to CBD and THC+CBD vapor when collapsed across time-points. Males: ↓ body temperature after exposure to THC (60–90 min) or CBD (60 min) vapor. ↓ locomotor activity following exposure to THC, CBD, and THC+CBD vapor. Activity following exposure to THC+CBD was lower compared to THC alone when collapsed across time-points (additive effect). *Hypothermic effects of THC vapor exposure were longer lasting in female rats. No differential effects of sex on THC, CBD, THC+CBD vapor effects on locomotor activity		
Adult Wistar rats (M/F)	THC, CBD, THC + CBD (1:4)	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	100 mg/ml THC; 400 mg/ml CBD	**Body temperature and locomotor activity** were measured with radiotelemetry for 4h after exposure to THC, CBD, or THC+CBD vapor	<u>Females:</u> ↓ body temperature after exposure to THC (30–210 min), CBD (30–240 min), and THC+CBD (30–240 min); THC+CBD effects were greater than THC or CBD alone. ↓ locomotor activity after exposure to THC (30-min), CBD (30-min), and THC+CBD (30–60 min). Activity following exposure to THC+CBD was lower compared to THC or CBD alone at the 30-min time-point (additive effect). <u>Males:</u> ↓ body temperature after exposure to THC (60–120 min), CBD (60–90 min), and THC+CBD (30–240 min). THC+CBD effects were greater than THC or CBD alone. — no effects of drug exposure on locomotor activity. *Hypothermic effects of THC and CBD vapor exposure were longer lasting in female rats. Female, but not male, rats showed hypolocomotion following THC, CBD, and THC+CBD vapor exposure (30-min time point).	*N.A.*	
Adult Wistar rats (M/F)	THC	4 × 10s puff every 5 min; (1st gen); 2–3 L/min air flow	30 min; twice daily for 4d	200 mg/ml	**Body temperature and nociception** were measured with rectal thermometer and tail	<u>Females:</u> ↓ body temperature after exposure to acute THC (30–120 min), and chronic THC (30-min). Temperatures after acute THC	*N.A.*	(Nguyen et al., 2018)

Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					waithdrawal latency for 4h after exposure to acute (1 session) or chronic (7th session) THC	were lower than after chronic THC. ↓ nociception after exposure to acute THC (30–240 min) and chronic THC (120-min). Males: ↓ body temperature after exposure to acute THC (30–60 min), and chronic THC (30–240 min). ↓ nociception after acute THC (30–60 min) and chronic THC (30–60 min). No differences in temperature or nociception between acute and chronic THC. *Female, but not male, rats showed tolerance to the hypothermic effects of THC after twice daily inhalation. THC reduces temperature more in female rats. Antinociceptive effects of THC vapor were similar in male and female rats.		
		1 × 6s puff every 5 min; (2nd gen); 2–3 L/min air flow	30 min; thrice daily for 4d	200 mg/ml	**Body temperature and nociception** were measured with rectal thermometer and tail withdrawal latency 35-min after exposure to acute (1 session) or chronic (10th session) THC	Females and Males: ↓ body temperature after exposure to acute THC and chronic THC. Temperatures after acute THC were lower (greater hypothermia) than after chronic THC. ↓ nociception after acute, but not chronic THC. –No differential effects of sex on effects of THC vapor exposure on antinociception.	*N.A.*	
Adult Sprague-Dawley rats (M)	THC	4 × 10s puff every 5 min; (1st gen); 1 L/min air flow	30 min	25 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry for 3.5h after exposure to THC vapor	↓ body temperature after exposure to THC (180–210 min). ↓ locomotor activity after exposure to THC (180–210 min).	Peak body temperature decreases were ~ 1°C lower after 5 mg/kg i.p. THC and hypothermic effects were longer lasting (60–210 min). No observed effects of THC i.p. on locomotor activity	*(Javadi-Paydar et al., 2019)*
			15m min, 4x repeated	12.5 mg/ml	**Body temperature and locomotor activity** were measured with radiotelemetry during	↓ body temperature after the third exposure to THC (180–270 min). ↑ locomotor activity after 1 exposure to THC (30-min),	*N.A.*	

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					repeated 15-min exposures to THC vapor (occurring every 45-min) and for an additional 1h (total 4.5h)	followed by ↓ locomotor activity after the fourth exposure to THC (270-min).		
Adult Wistar rats (M)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	12.5– 200 mg/ml	**Intravenous oxycodone (OXY) self-administration** was measured under fixed-ratio 1 schedule of reinforcement in an 8h session after acute exposure to THC vapor.	↓ OXY self-administration after exposure to 100 mg/ml (1-hr) and 200 mg/ml (1–5h) THC. No effects of 12.5 and 25 mg/ml THC were observed on OXY self-administration. Pretreatment with CB1 antagonist (SR141716) blocked this effect.	The reduction in oxycodone self-administration by 200 mg/ml THC vapor was comparable to 10 mg/kg i.p. and, while 5 mg/kg i.p. THC had no effect.	(Nguyen et al., 2019b)
		1 × 10s puff every 5 min; (2nd gen); 1 L/min air flow	30 min	N.S.	**Intravenous OXY self-administration** was measured under fixed-ratio 1 schedule of reinforcement in an 1h session after exposure to THC vapor.	↓ OXY self-administration after exposure to THC vapor.	*N.A.*	
Adult Wistar rats (M/F)	THC, OXY, THC + OXY	1 × 10s puff every 5 min; (2nd gen); 1 L/min air flow	30 min	50 mg/ml THC; 100 mg/ml OXY	**Nociception** was measured as tail withdrawal latency 35–120 min after exposure to THC vapor.	Females and Males: ↓ nociception after exposure to THC (35–120 min), OXY (35-min), and THC+OXY (35–60 min). THC+OXY effects at 35-min were greater than THC or OXY alone. *No differential effects of sex on the antinociceptive effects of THC/OXY vapor.	Similar increases in antinociception were observed after injection with 5 mg/kg, i.p. THC and 2 mg/kg, s.c. OXY. THC+OXY, i.p. effects at 35-min were greater than THC or OXY alone.	
Adolescent Wistar rats (M/F)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	100 mg/ml	**Body temperature** was measured with radiotelemetry after exposure to acute THC vapor.	Females: ↓ body temperature after exposure to THC vapor (60–270 min). Males: ↓ body temperature after exposure to THC vapor (30–210 min). *Adolescent males showed faster recovery from the hypothermic effects of acute THC vapor compared to females.	*N.A.*	(Nguyen et al., 2019a)
					Body temperature and locomotor activity was measured with radiotelemetry during exposure to chronic THC	Females: ↓ body temperature after acute exposure to THC vapor (60–300 min), an effect which dissipated by chronic exposure day 4.	*N.A.*	

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
					vapor (twice daily for 10 days).	Males: ↓ body temperature after acute exposure to THC vapor (30–180 min). After subsequent THC exposures (days 2–10), body temperature decreased only transiently (60-min timepoint only). Females and Males: ↑ locomotor activity in the first 60 minutes, followed by ↓ activity from hour 2–4. Locomotor activity remained sensitive to THC across multiple exposures. *Females, but not males, developed tolerance to the hypothermic effects of chronic twice daily THC exposure.		
Adult Wistar rats (M/F)	THC	4 × 10s puffs every 5 min; (1st gen); 1 L/min air flow	30 min	25–100 mg/ml (F), 100–200 mg/ml (M)	**Body temperature** was measured with radiotelemetry after acute THC in adult rats who were previously exposed to chronic THC vapor (twice daily for 10 days) in adolescence (PND 35–39 and PND 42–46).	Females: ↓ body temperature was reduced after exposure to 25–100 mg/ml in animals with a history of chronic adolescent PG exposure (controls); concentration-dependent effect. In animals with a history of chronic adolescent THC vapor exposure, only 100 mg/ml THC reduced body temperature. Males: ↓ body temperature was reduced after exposure to 100–200 mg/ml in animals with a history of chronic adolescent PG exposure (controls); concentration-dependent effect. In animals with a history of chronic adolescent THC vapor exposure, only 200 mg/ml THC reduced body temperature. *100 mg/ml THC caused hypothermia in adult female, but not adult male, rats who were exposed to chronic THC vapor in adolescence.	*N.A.*	
Adult Wistar rats (M/F)	THC	4 × 10s puffs every 5 min; (2nd gen); 1 L/min air flow	30 min; twice daily for 10d	100 mg/ml	**Feeding and body weight** was measured in adult rats who were previously exposed to chronic THC vapor in adolescence (PND 35–39 and PND 42–46).	Females: __ no effects of prior chronic adolescent THC exposure on food intake or body weight Males: ↓ food intake in males with a history of chronic adolescent THC exposure __ no effects of a history of chronic adolescent THC vapor exposure on body weight *Male, but not female, rats who were exposed to chronic THC	*N.A.*	

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Species/Sex	Drug formulation	Exposure Parameters	Exposure duration	THC Dose (mg) or Concentration (mg/ml)	Behavioral Test Methods	Behavioral Outcome	Route Comparison	Ref.
						vapor in adolescence show reduced food intake in adulthood.		
					Intravenous OXY self-administration and drug discrimination was measured adult rats who were previously exposed to chronic THC vapor in adolescence (PND 35–39 and PND 42–46).	Males and Females: – no effects of prior chronic adolescent THC exposure on OXY self-administration or OXY drug discrimination. *No differential effects of sex on the effects of chronic adolescent exposure to THC vapor on OXY self-administration.	*N.A.*	
Adult Wistar rats (F)	THC	4 × 10s puffs every 5 min; (2nd gen); 1 L/min air flow	30 min; twice daily for 10d	100 mg/ml	**Intravenous fentanyl self-administration** was measured under fixed-ratio 1 schedule of reinforcement in an 8h session in adult rats who were previously exposed to chronic THC vapor in adolescence (PND 35–39 and PND 42–46).	↑ fentanyl self-administration in female rats with chronic adolescent THC exposure.	*N.A.*	

(M) = Males, (F) = Females; N.S. = Not Stated; N.A. = Not applicable; THC = Delta-9-tetrahydrocannabinol; CBD = cannabidiol; OXY = oxycodone; i.p. = intraperitoneal; s.c. = subcutaneous. Symbols ↑ (increased), ↓ (decreased), and – (no change) denote direction of observed effects.

* Asterisk denotes a summary of sex differences results.

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