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Cannabis Extract Composition Determines Reinforcement in a Vapor Self-Administration Paradigm

Anand K. Muthusamy
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125
Review of Freels et al.

Introduction

The legalization of cannabis and shifting cultural attitudes have driven an increase in cannabis use and the proliferation of vapor delivery devices. The DSM-V recognizes "cannabis use disorder" under the umbrella of substance use disorders, but its neural mechanisms require greater clarity (Peters et al., 2020). Debate in the scientific community and the public sphere alike primarily asks, "is cannabis addictive?" and "are there negative effects from chronic use?" The first issue magnifies the second: if users compulsively seek cannabis or become dependent, then safe regimens become difficult to maintain.

Drug abuse studies in human populations generally are confounded by use of other drugs, medical history, and varying genetic background. Self-administration in animal models sidesteps these issues and has good construct validity given the volitional consumption (Koob et al., 2012). Unlike cocaine and opioid self-administration studies, however, self-administration of cannabis or Δ^9-tetrahydrocannabinol (THC) alone has been notoriously difficult to establish across several species because of THC's weak rewarding effect and aversive effects at high doses (Justinova et al., 2005; Fuchs et al., 2019). Although THC is the primary psychoactive compound in cannabis, extracts may have over 120 other phytocannabinoids, including cannabidiol (CBD), which has its own effects as an inverse agonist at cannabinoid receptors (Ibsen et al., 2017). Further complicating self-administration is the varying pharmacokinetics of different delivery methods. In particular, intravenous delivery, which is used for other addictive drugs, leads to fast infusion rates that trigger aversive effects for THC (Carbuto et al., 2012).

Freels et al. (2020) addressed these long-standing issues by designing a vapor-delivery method to successfully establish cannabis self-administration in rodents. Their paradigm bears the greatest similarity to human use to date by allowing volitional and titratable vapor delivery of cannabis extracts (MacCallum and Russo, 2018). The National Institute on Drug Abuse drug supply program provided whole cannabis extract enriched with either THC (CAN_{THC}) or CBD (CAN_{CBD}). In the apparatus, rats could nose-poke to activate one of two ports indicated by a 60 s light cue. When one port was activated, one of three vapors was delivered: organic solvent vehicle, CAN_{THC}, or CAN_{CBD}; when the other port was activated, nothing was delivered.

CAN_{THC} uniquely reinforces self-administration by acting on cannabinoid receptor type 1 (CB_1)

Freels et al. (2020) demonstrated that Sprague Dawley rats will stably self-administer CAN_{THC} and perform more work for a single delivery of CAN_{THC} vapor than for CAN_{CBD} or vehicle. Across fixed ratios of nose-pokes to vapor deliveries, rats maintained a consistent number of CAN_{THC} vapor deliveries in each session, and the number of deliveries was significantly higher than for CAN_{CBD} or vehicle (~5 to ~12 deliveries/day, a baseline for nose-poking). In all experiments, Freels et al. (2020) observed some level of nose-poking for the vehicle delivery, suggesting some interest in the cue light and/or solvent vapor. Even under the 1:1 ratio, however, rats did not respond significantly more for CAN_{CBD} than for vehicle. Furthermore, when the rats faced a sequentially increasing number of nose-pokes required to earn vapor delivery, they worked significantly more for CAN_{THC}, but not for CAN_{CBD}, than for vehicle. Notably, rats nose-poked for CAN_{THC} most often in the first 15 min of each 1 h session. These results suggest that rats learn to nose-poke at a certain rate to achieve a desired THC level. Maintaining CAN_{THC} consumption under a mounting workload points to the drug's reinforcing efficacy and is comparable with the human motivation to devote time and effort to seek an appealing stimulus (Fuchs et al., 2019).

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Correspondence should be addressed to Anand K. Muthusamy at amuthusa@caltech.edu.

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Freels et al. (2020) found that systemic injection of AM251, a CB_1-selective antagonist, reduced the CAN_{THC} vapor seeking rate to vehicle control levels, whereas the CAN_{CBD} group was unaffected. While CB_1 is widely expressed across the mammalian brain, a well-characterized midbrain reward mechanism implicated in the self-administration of other addictive substances likely underlies CAN_{THC}'s effect (Gardner, 2005). THC acts as partial agonist of CB_1, which is abundantly expressed in VTA GABAergic terminals (Sperlágh et al., 2009). In the VTA, the activation of CB_1 diminishes the GABAergic inhibition of dopaminergic neurons that project to the NAc (Gardner, 2005; Peters et al., 2020). The resulting increase in dopaminergic tone in the NAc is rewarding and can establish drug addiction (Peters et al., 2020).

THC:CBD ratio in extracts determines selectivity in self-administration and presentation of the tetrad response

Surprisingly, although rats were not willing to work as hard to earn CAN_{CBD} as they were to earn CAN_{THC}, they self-administered CAN_{CBD} more selectively. In the behavior apparatus, the rats could learn which port provided any vapor as opposed to no outcome. Only the rats earning CAN_{CBD} achieved a fraction of nose-pokes at the active port that was significantly greater than the vehicle group. Quantification of cannabinoid concentrations in the rat brain likely explains this finding. Each of the two cannabis extracts had a small quantity of the nonenriched compound. CAN_{THC} extract had a THC concentration nearly 30× that of CAN_{CBD} and a CBD concentration only 1/40 that of CAN_{CBD}. Nonetheless, after self-administration, brain THC concentrations were similar regardless of which extract was delivered, whereas the concentration of CBD was ~3× greater in rats receiving CAN_{CBD} than in those receiving CAN_{THC}. These results demonstrate that rats achieve pharmacologically relevant increases in brain THC with both extracts; the enrichment of THC in the CAN_{CBD} group might result from inhibition of THC metabolism by CBD (Jones and Pertwee, 1972). Furthermore, because THC disrupts spatial memory and acquisition of operant tasks in rats, it may increase the error in discrimination (Varvel et al., 2001; Delatte et al., 2002). Finally, CBD counteracts the psychotropic and aversive effects of THC particularly through action in the ventral hippocampus (Hudson et al., 2019). A balance between THC-driven motivation and CBD-protected learning may therefore underlie the discrimination disparity across CAN_{THC} and CAN_{CBD} groups.

In a separate experiment, the rats' locomotion and metabolic parameters were measured over 10 d of fixed-ratio self-administration. Only rats that self-administered CAN_{THC} exhibited some features of the classical physiological "tetrad" response: lowered spontaneous activity, antinociception, hypothermia, and catalepsy (Metna-Laurent et al., 2017). Rats self-administering CAN_{THC} spent more time inactive than those receiving CAN_{CBD} but also displayed significantly greater food consumption and energy expenditure. In contrast, locomotor and metabolic signatures were indistinguishable in the CAN_{CBD} and vehicle groups. This demonstrates that the extracts have different effects on some internal states (e.g., arousal and appetite). Still, the mechanism that relates drug action to internal state and physiological adaptations that lead to self-administration selectivity or chronic drug seeking is not yet clear.

Self-administration of CAN_{CBD} is more resistant to extinguishing while CAN_{THC} elicits stronger reinstatement, raising questions about the underlying circuit adaptations

Freels et al. (2020) trained another cohort of rats to self-administer vapor over 19 d and then continued sessions with both ports set as inactive over 7 d. The CAN_{CBD} group, but not the CAN_{THC} group, required significantly more trials than the vehicle group to extinguish nose-poking (defined as a 50% decrease in nose-pokes at the previously active port since the last session with vapor delivery). Transitioning the rats off of the vapor thus raised an apparent inconsistency with the prior results: rats were more resistant to extinguishing the seeking of CAN_{CBD} despite their greater motivation to consume CAN_{THC}. This observation is especially curious given that CBD disrupts the association between rewarding effect and the spatial location where rats consume cocaine or opioids (de Carvalho and Takahashi, 2017; Mahmud et al., 2017). The result might be explained by a difference in learning rates due to reward prediction error for dopamine reinforcement (Glimcher, 2011). The light cue or vapor smell may be more salient to the CAN_{THC} group because they experience the reinforcing effect of higher THC concentrations immediately. The CAN_{THC} group may have then experienced a greater unexpected result under extinguishing conditions, eliciting a faster rate of learning to stop nose-poking.

Finally, to test the reinstatement of vapor seeking, Freels et al. (2020) provided an additional session after extinction, in which nose-poking the previously active port triggered the light cue, but no vapor delivery. Only rats previously receiving CAN_{THC} increased their nose-poking relative to the vehicle group. This result indicates a sustained stronger motivation to seek CAN_{THC} and is consistent with the previous results indicating that CAN_{THC} has a greater reinforcing efficacy compared with that of CAN_{CBD}. This drive to seek CAN_{THC} could be motivated by reward-seeking, withdrawal avoidance, or a combination of both factors (Fuchs et al., 2019).

The study of cannabis use disorder is now challenged with distinguishing the actions of each cannabis constituent in the development and reinforcement of maladaptive behaviors. Future work should characterize the pharmacokinetics for the method developed by Freels et al. (2020), given that human use of electronic cannabis vaporization demands considerable optimization (Hazekamp et al., 2006). Then, one could determine whether synthetic agonists, purified THC and CBD, or cannabis extracts are sufficient to establish self-administration. The work by Freels et al. (2020) also raises questions about reward encoding and prediction mechanisms. The critical question for addiction studies remains: what, if any, factor could transition an animal from controlled to compulsive cannabis seeking that forgoes well-being (Everitt et al., 2008)? Freels et al. (2020) have provided the behavioral neuroscience field with a method to address these questions with excellent fidelity to the human experience of cannabis use.

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