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Smoked cannabis reduces peak cocaine plasma levels and subjective effects in a controlled drug administration study of polysubstance use in men

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Abstract

Background: Despite the high prevalence of polysubstance use, outcomes and potential risks associated with common drug combinations are not well characterized. Many individuals who use cocaine also use cannabis, yet little is known about how interactions between the two drugs might contribute to continued co-use.

Methods: The aim of this double-blind, placebo-controlled study was to determine the physiological and subjective effects of smoked cannabis with smoked cocaine, to identify variables that may contribute to the continued use of this drug combination. Healthy, non-treatment seeking volunteers who reported smoking both cocaine and cannabis (N = 9, all males) completed a 13-day inpatient protocol. On session days, cannabis [0.0 or 5.6 % tetrahydrocannabinol (THC)] was administered 28 min prior to cocaine (0, 12, or 25 mg). Dependent measures included

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Declaration of Competing Interest

The authors declare that they have no competing interests or disclosures with this publication. Outside of this work, ZDC reports receiving study drug from Canopy Growth Corp and True Terpenes, and study-related materials from Storz & Bickel. MH serves on the Scientific Advisory Board for Pleo Pharma.

CRediT authorship contribution statement

ZDC received funding for this study and was responsible for study concept and design with assistance from MH and RWF. CHM drafted the manuscript. ZDC, MH, RWF, JM, and GB performed essential study procedures. All authors critically reviewed content and approved the final version for publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109757.

pharmacokinetic assessment of THC and cocaine and their respective metabolites, in addition to subjective and cardiovascular effects.

Results: Active cannabis (5.6 % THC) increased plasma levels of THC and the metabolite 11-nor-9-carboxy-Δ9-THC (THCCOOH), as well as subjective ratings of cannabis effects and heart rate relative to inactive cannabis. Cocaine dose-dependently increased plasma cocaine and metabolites and subjective ratings of cocaine effects. Active cannabis pre-treatment decreased plasma levels of cocaine and metabolites. Furthermore, active cannabis attenuated cocaine-related reductions in 'Hunger' and 'Calm.'

Conclusions: Cannabis pre-treatment altered the subjective experience of smoked cocaine and reduced peak plasma levels of cocaine. Future studies should explore additional doses of each drug and whether these changes also impact cocaine's reinforcing effects.

Keywords

Polysubstance Use; Cocaine; Cannabis; Pharmacokinetics; Subjective Effects

1. Introduction

Individuals with substance use disorders rarely report the use of a single substance, but rather endorse co-use of a variety of illicit and licit drugs (Crummy et al., 2020). Studies within behavioral pharmacology have aided in identifying pharmacotherapies for individuals that have a mono-substance use disorder (Elias and Kleber, 2017; Haney and Spealman, 2008). However, investigations often do not address potential issues and treatment strategies related to polysubstance use. For instance, modafinil has shown efficacy for treating cocaine dependence, but in some studies, these effects occurred only in patients who were not also alcohol dependent (Anderson et al., 2009; Foltin et al., 2016; Haney et al., 2021). Determining the effect profile and health risks of co-administered drugs in the laboratory is an important step to advance treatments for individuals with polysubstance use disorders.

Cannabis is the most widely used federally illicit substance in the United States and Europe (EMCDDA, 2022; U.S. Department of Health and Human Services, 2010). It is also commonly used in conjunction with other illicit and licit substances. Findings from the 2020 National Survey on Drug Use and Health demonstrate that about 84 % of the population who report using other illicit substances in the past year also reported past year cannabis use (U.S. Department of Health and Human Services, 2010). In cannabis users, about 47 % report use of other illicit substances, thus endorsing polysubstance use. Use of cannabis with cocaine is well-established (Abelson and Miller, 1985; Goode, 1969), with a recent meta-analysis finding that the prevalence of concurrent cannabis use among people who use cocaine to be around 64 % (Liu et al., 2018).

The effects from co-use of cocaine and cannabis are unclear. For example, some have hypothesized that these drugs are combined to prolong effects, decrease aversive effects, or enhance positive effects relative to when the drugs are used independently (Barrett et al., 2006; Foltin and Fischman, 1992; Lukas et al., 1994). Another hypothesis is that commonly co-administered drugs interact to affect behavioral patterns associated with regulation of

continued use of one or the other drug (Leri et al., 2003). This notion is supported by anecdotal reports of women with cocaine dependence who smoke cannabis during pregnancy to help curb urges to smoke cocaine (Rosenbaum and Irwin, 1998). Furthermore, in a recent observational study of people who smoke cocaine, intentional use of cannabis to reduce cocaine use was associated with a lower frequency of cocaine use (Socías et al., 2017). However, others have reported that concurrent cannabis use is associated with a heavier pattern of cocaine use and higher scores on the Addiction Severity Index (Lindsay et al., 2009). In pre-clinical studies, the acquisition of cocaine self-administration in adult female, but not male, rats was augmented by exposure to a cannabinoid receptor agonist during adolescence (Higuera-Matas et al., 2008). Cannabinoid receptor agonists, which include Δ9-tetrahydrocannabinol (THC), have also been shown to increase cocaine-seeking behavior in animal models of addiction (Justinova et al., 2009).

Understanding the nature of cannabis-cocaine interactions will provide clinically relevant information that identifies abuse liability and health risks while laying the groundwork for developing treatment strategies. Initial laboratory studies indicate that acute cannabis exposure may enhance behavioral and physiological responses to insufflating or intravenous cocaine (Foltin and Fischman, 1989; Foltin et al., 1995, 1987, 1993; Lukas et al., 1994). However, these early studies did not consistently use a cannabis-only condition in the study design to assess potential additive effects of the drugs. More importantly, prior studies did not investigate the use of smoked cocaine in combination with cannabis, a combination that is reported in more than a quarter of people who use both cocaine and cannabis (Liu et al., 2021). Although this combination is commonly endorsed, use of smoked cocaine with cannabis has never before been systematically investigated in controlled laboratory studies. Here, we examined interactions of smoked cocaine and cannabis, i.e., an aerosol generated by heating the cocaine base or cannabis joint, in an inpatient study.

This study was designed to compare pharmacokinetic, subjective ratings, and cardiovascular effects of cannabis (0.0 or 5.6 % THC) smoked 28 min prior to repeated administration of smoked cocaine (0, 12, or 25 mg), when cannabis-elicited effects peak (Haney et al., 2005), thus generating a dose-effect function for cocaine's effects in the presence and absence of cannabis over 6 sessions. We hypothesized, based on a prior report with insufflated cocaine (Lukas et al., 1994), that active cannabis would increase cocaine plasma levels and subjective reports of intoxication and abuse liability in addition to increasing heart rate relative to placebo cannabis.

2. Methods

2.1. Study design

This study used a within-subjects design in an inpatient setting over a 13-day span. On day 1, volunteers meeting criteria for DSM-IV cocaine dependence acclimated to an inpatient research unit. Participants smoked combinations of cannabis (0 % or 5.6 % THC) and cocaine (0, 12, or 25 mg) over 6 laboratory session days; each session tested one cocaine - cannabis dose combination. On each session day, cocaine was smoked 28 min after cannabis, and thereafter at 14-minute intervals for 3 additional cocaine administrations (i.e., total of 4 cocaine administrations per session). Pharmacokinetic, cardiovascular, and

self-report measures were collected before drug administration and at regular intervals after cannabis and cocaine administration. Sessions ended 30 min after the final cocaine administration. On day 13, participants were debriefed and discharged. The inpatient unit was a locked, supervised facility and protocols were in place to ensure that no psychoactive substances were brought to the research unit.

2.2. Study participants

Healthy male and non-pregnant female volunteers, 21–45 years of age were recruited through advertisements placed in New York City newspapers and by word-of-mouth. Both male and female volunteers were screened, however only males were eligible and enrolled. Eligible volunteers had no major medical or psychiatric illness, and no current use of prescribed medications. Participants had cocaine dependence and used cannabis, as assessed by the DSM-IV and positive urine toxicology tests. Participants were excluded if they were seeking treatment for drug use, had a history of serious adverse responses to the study drugs, a history of contraindications for receiving study drugs including seizure and cardiac conditions, or met DSM-IV criteria for psychiatric disorders including a substance dependence disorder other than for cocaine, cannabis, or tobacco. Of 13 participants recruited into the study, 9 completed the study and were included in the final analysis. Informed consent was obtained prior to study enrollment. All procedures were approved by the Institution Review Board of the New York State Psychiatric Institute and were in accordance with the Declaration of Helsinki.

2.3. Drugs

Active (5.6 % THC) and inactive (0.0 % THC) cannabis cigarettes were provided by the National Institute on Drug Abuse. Participants received one cannabis cigarette at each session under double-blind and randomized conditions. Cannabis was smoked, i.e., an aerosol generated by heating the cannabis joint was inhaled, using standardized paced-puffing procedures (Foltin et al., 1987). Briefly, participants were told to “light” the cigarette (30 s), “prepare” (5 s), “inhale” (5 s), “hold [in lungs]” (10 s), and “exhale” every minute until 75 % of the cigarette was smoked. The cannabis smoking procedure began 28 min prior to cocaine administration so that cocaine administration occurred near the time of peak cannabis effects.

Cocaine HCl was purchased from Mallinckrodt (St. Louis, Missouri). Pellets of cocaine base were manufactured by the pharmacy at the New York State Psychiatric Institute. Fixed dosing of placebo (0 mg) and two active doses of smoked cocaine (12 and 25 mg) were used to examine potential dose-dependent effects; we selected these doses based on their characterization in our previous studies (Haney et al., 2006). The cocaine (12 or 25 mg) or placebo doses were administered repeatedly at 28, 42, 56, and 70 min following cannabis administration. Cocaine was smoked, i.e., an aerosol generated by heating the cocaine base was inhaled, in a single inhalation over 30 s using glass stem pipes. A study physician or nurse held and lit the pipe with a lighter and vaporization was accomplished after the blindfolded subject was cued to inhale (Foltin et al., 1990). Placebo was inhaled as heated air through an empty pipe. Participants were blindfolded immediately prior to smoking to obstruct visual cues and maintain blinding of the dose condition.

2.4. Pharmacokinetic measures

Plasma levels of THC, cocaine and their metabolites were quantified using capillary gas chromatography/mass spectrometry (HP5988) in the Analytic Pharmacology Laboratory at the New York State Psychiatric Institute as previously described (Cooper and Haney, 2009; Haney et al., 2010). Briefly, the procedure utilizes the negative chemical ionization of the derivitized compounds and deuterated internal standards with selected ion monitoring and methane/ammonia as the reactant gas. Blood (7.5 mL) was drawn 30 min prior to cannabis administration, and thereafter at 14, 32, 46, 60, 74, and 88 min following cannabis administration. To draw blood, a 20-gauge catheter (QuikCath®; Treavenol Laboratories, Deerfield IL, USA) was inserted into an arm vein at the beginning of each session. Plasma was centrifuged, frozen and later analyzed for Δ9-THC (THC), 11-nor-9-carboxy-Δ9-THC (THCCOOH), cocaine, benzoylecgonine (BZ), and ecgonine methyl ester (EME).

2.5. Cardiovascular measures

Blood pressure and heart rate were monitored at regular, two-minute intervals using a blood pressure cuff placed on the participants' non-dominant arm, with connections to a Sentry II automated vital signs monitor (NBS Medical Services, Costa Mesa, CA). Cardiovascular measures used in the analysis were recorded immediately before blood draws occurring at – 30 (baseline) and 14, 32, 46, 60, 74, and 88-minute time points relative to cannabis administration. Relative to cocaine administration, the 32, 46, 60, and 74-minute time points occurred 4 min after each of the 4 cocaine doses.

2.6. Subjective drug and mood effects

Subjective drug and mood effects were obtained immediately after blood draws occurring at – 30 (baseline) and 14, 32, 46, 60, 74, and 88-minute time points relative to cannabis administration. Self-report included a Cannabis Rating Form (CRF), which was not administered at the – 30 time point, and visual analog scales (VAS), administered at all time points. Both the CRF and VAS comprised a series of 100 mm long lines each labeled with "not at all" and "extremely" on either end. All CRF and VAS items were presented individually on a computer screen and participants indicated ratings for respective items using a mouse. CRF items asked participants to rate the strength of the cannabis, if the cannabis was good or bad, if they liked the cannabis and if they wanted to take the cannabis again (Haney et al., 2005). VAS items specific for cocaine effects were grouped in clusters, which yielded the average score of collinear VAS items according to previous work (Evans et al., 2002; Haney et al., 2006). These clusters included Good Cocaine Effect ('Stimulated,' 'High,' and 'Good drug effect'), Bad Cocaine Effect ('Depressed,' 'Sedated,' 'Anxious,' 'Tired,' 'Irritable,' 'Confused,' and 'Bad drug effect'), Cocaine Quality ('I liked this choice,' 'This choice was potent,' and 'This choice was high quality'), Focus ('Focused,' 'Calm,' and 'Able to concentrate'), and Social ('Social,' 'Talkative,' 'Confident,' and 'Alert'). In addition to these five VAS clusters, one VAS measure examined willingness to pay for the cocaine dose from $0 to $25, and four additional VAS items assessed drug craving: 'I want cocaine,' 'I want cannabis,' 'I want tobacco,' and 'I want alcohol.' One final VAS item, 'Hungry,' examined hunger.

2.7. Statistical analysis

Dependent measures were analyzed with repeated-measures ANOVA using cannabis and cocaine dose as within-subject factors. The dependent measures were analyzed in two steps. First, multifactorial ANOVAs examined the time course between different doses of cocaine and cannabis, with significant results presented in Supp. Table 1. If the multifactorial ANOVAs included a significant time by cannabis or cocaine interaction, we proceeded with additional ANOVAs examining peak change from baseline (or peak effect in the case of the CRF, which does not measure a baseline) in addition to area under the curve (AUC) for each of the six drug conditions (cannabis or placebo with 0, 12 or 25 mg cocaine). Dependent measures that resulted in significant follow-up peak change ANOVAs are presented in the main results, with AUC included in the main pharmacokinetic results. All ANOVAs were tested for sphericity using the Mauchley Sphericity Test. Dose-dependent findings were operationalized by linear main effects of cocaine dose and effect sizes were assessed with partial eta squared (η_p^2). For two measures, the multifactorial ANOVAs did not result in significant interaction terms, but did result in significant main effects of cannabis, and these results are presented in Supplementary material (Supp. Fig. 1). Dependent measures were checked for skewness and kurtosis and passed normality tests with the Shapiro-Wilk test (Supp. Table 2). All analyses were conducted with SPSS (version 26; SPSS Inc., Chicago, IL).

3. Results

3.1. Demographic characteristics

A total of 9 participants, all males, completed the 13-day in-patient protocol and were included in our analysis. Females were screened but did not enroll into the study. An additional 4 participants did not complete the study. Two were withdrawn due to cardiovascular abnormalities detected after enrollment, and two withdrew for personal reasons unrelated to drug administration. Table 1 shows that in addition to regular cocaine and cannabis use, the participants averaged 4 standard drinks of alcohol three times a week and all smoked tobacco cigarettes (range: 3–20 cigarettes per day).

3.2. Pharmacokinetics

To determine whether cannabis affects cocaine plasma levels, or vice versa, we measured plasma levels of THC, cocaine, and their metabolites under fixed dosing conditions (Fig. 1). As expected, active cannabis (5.6 % THC) significantly increased peak plasma levels of THC ($F_{1,8} = 14.29$, $p = 0.007$, $\eta_p^2 = 0.671$) (Fig. 1A) and the THC metabolite THCCOOH ($F_{1,8} = 29.97$, $p = 0.007$, $\eta_p^2 = 0.671$) (Fig. 1B) relative to inactive cannabis (0.0 % THC). These effects were also found across sessions, with increases in overall plasma levels of THC ($F_{1,8} = 18.97$, $p = 0.002$, $\eta_p^2 = 0.703$) (Fig. 1A) and THCCOOH ($F_{1,8} = 99.67$, $p < 0.001$, $\eta_p^2 = 0.882$) as assessed by AUC (Fig. 1B). Cocaine (12, 25 mg) dose-dependently increased peak plasma levels of both cocaine ($F_{1,8} = 36.87$, $p < 0.001$, $\eta_p^2 = 0.840$) (Fig. 1C) and the cocaine metabolite BZ ($F_{1,8} = 60.96$, $p < 0.001$, $\eta_p^2 = 0.884$) (Fig. 2D), in addition to overall cocaine ($F_{1,8} = 28.26$, $p < 0.001$, $\eta_p^2 = 0.780$) (Fig. 1C) and BZ levels ($F_{1,8} = 69.61$, $p < 0.001$, $\eta_p^2 = 0.897$) (Fig. 1D) as assessed by AUC. However, for AUC

cocaine plasma levels, Mauchly's test indicated that the assumption of sphericity had been violated, ($X^2(2) = 8.95$, $p = 0.011$). The doses of cocaine did not affect cannabinoid plasma levels when administered after active cannabis. However, pretreatment with active cannabis significantly reduced peak plasma levels of cocaine ($F_{1,8} = 6.48$, $p = 0.038$, $\eta_p^2 = 0.481$), but not AUC cocaine levels ($F_{1,8} = 4.10$, $p = 0.078$, $\eta_p^2 = 0.339$) (Fig. 1C). The active cannabis pretreatment, relative to placebo cannabis, also significantly reduced both peak BZ levels ($F_{1,8} = 11.36$, $p = 0.010$, $\eta_p^2 = 0.587$) and overall BZ levels ($F_{1,8} = 7.25$, $p = 0.027$, $\eta_p^2 = 0.475$, cannabis and cocaine interaction;($F_{1,8} = 6.47$, $p = 0.034$, $\eta_p^2 = 0.447$, main effect of cannabis) (Fig. 1D).

3.3. Subjective measures

Subjective responses for active cannabis (5.6 % THC) were greater than inactive cannabis (0.0 % THC), as assessed by the Cannabis Rating Form (CRF), (Fig. 2). Specifically, participant ratings for the strength of the cannabis (peak effect: ($F_{1,8} = 16.24$, $p = 0.004$, $\eta_p^2 = 0.670$), Fig. 2A; AUC: ($F_{1,8} = 26.66$, $p = 0.001$, $\eta_p^2 = 0.769$, Supp. Fig. 1A), ratings of "Good cannabis" (peak effect: ($F_{1,8} = 16.53$, $p = 0.004$, $\eta_p^2 = 0.674$, Fig. 2B; AUC:($F_{1,8} = 16.04$, $p = 0.004$, $\eta_p^2 = 0.667$, Supp. Fig. 1B), and willingness to take again (peak effect: ($F_{1,8} = 9.06$, $p = 0.017$, $\eta_p^2 = 0.531$, Fig. 2C; AUC:($F_{1,8} = 9.67$, $p = 0.014$, $\eta_p^2 = 0.547$, Supp. Fig. 1C) were greater for active relative to inactive cannabis. None of the subjective responses to cannabis on the CRF were affected by inclusion of cocaine.

On the visual analog scale (VAS), cocaine dose-dependently increased participant ratings of Good Cocaine Effect (peak change: ($F_{1,8} = 28.63$, $p < 0.001$, $\eta_p^2 = 0.782$, Fig. 3A; AUC: ($F_{1,8} = 26.45$, $p < 0.001$, $\eta_p^2 = 0.768$, Supp. Fig. 2A), Cocaine Quality (peak change: ($F_{1,8} = 39.27$, $p < 0.001$, $\eta_p^2 = 0.831$, Fig. 3B; AUC: ($F_{1,8} = 29.85$, $p < 0.001$, $\eta_p^2 = 0.789$, Supp. Fig. 2B), and Willingness to Pay (peak change: ($F_{1,8} = 11.60$, $p = 0.009$, $\eta_p^2 = 0.592$, Fig. 3F; AUC: ($F_{1,8} = 16.25$, $p = 0.004$, $\eta_p^2 = 0.670$, Supp. Fig. 2F). These subjective responses to cocaine were not affected by inclusion of cannabis.

However, while cocaine reduced ratings of Hunger (peak: ($F_{1,8} = 7.45$, $p = 0.026$, $\eta_p^2 = 0.482$, Fig. 3E; AUC: ($F_{1,8} = 7.97$, $p = 0.022$, $\eta_p^2 = 0.499$, Supp. Fig. 2E), Calm (peak change: ($F_{1,8} = 14.83$, $p = 0.005$, $\eta_p^2 = 0.650$, Fig. 3D; AUC: ($F_{1,8} = 11.64$, $p = 0.009$, $\eta_p^2 = 0.593$, Supp. Fig. 2D), and Focus (peak change: ($F_{1,8} = 7.76$, $p = 0.024$, $\eta_p^2 = 0.492$, Fig. 3C; AUC: ($F_{1,8} = 15.21$, $p = 0.005$, $\eta_p^2 = 0.655$, Supp. Fig. 2C), the active cannabis condition increased ratings of Hunger (peak change: ($F_{1,8} = 6.17$, $p = 0.038$, $\eta_p^2 = 0.436$, Fig. 3E; AUC: ($F_{1,8} = 8.17$, $p = 0.021$, $\eta_p^2 = 0.505$, Supp. Fig. 2E). Active cannabis also increased ratings of Calm and Tired, while reducing ratings of Talkative in multifactorial ANOVAS that incorporated time as a within-subjects factor (Supp. Fig. 3). Ratings for Cocaine Craving, which were increased by cocaine in the multifactorial ANOVA, did not reach significance in the follow-up ANOVAs, nor were they affected by the active cannabis condition (Supp. Table 1).

3.4. Cardiovascular measures

Active cannabis (5.6 % THC) increased heart rate responses relative to inactive cannabis (0.0 % THC) (peak change: ($F_{1,8} = 5.45$, $p = 0.048$, $\eta_p^2 = 0.405$, Fig. 4; AUC: ($F_{1,8} = 9.06$, $p =$

0.017, $\eta_p^2 = 0.53$, Supp. Fig. 4). Cocaine also dose-dependently increased heart rate overall as assessed by AUC ($F_{1,8} = 13.27$, $p = 0.007$, $\eta_p^2 = 0.624$, Supp. Fig. 4), but did not significantly affect peak changes in heart rate (Fig. 4). No effects on systolic or diastolic blood pressure were observed for either cannabis or cocaine (data not shown) and neither cannabis nor cocaine altered the cardiovascular effects of the other drug.

4. Discussion

The current study examined the behavioral and physiological effects of experimenter-administered cannabis smoked prior to cocaine administration to identify variables that may contribute to the continued co-use of these drugs. Cannabis (5.6 % THC) attenuated peak plasma levels of cocaine and the cocaine metabolite BZ in addition to the overall plasma levels of BZ as assessed by area under the curve. However, this pharmacokinetic interaction did not have widespread effects on subjective drug ratings or cardiovascular outcomes. Nonetheless, cannabis did attenuate some of cocaine's subjective effects, consistent with the reductions in cocaine and metabolite plasma levels, including cocaine-induced reductions in appetite and feelings of calm. Additionally, administration of cannabis produced the same effects on heart rate with or without the inclusion of cocaine (12, 25 mg).

Few studies in either humans or laboratory animals have examined the pharmacokinetic interaction of cocaine and cannabinoids (Daldegan-Bueno et al., 2021). Only one prior report has examined the pharmacokinetics of this drug combination, but with insufflating as opposed to smoked cocaine. In that study, smoked cannabis 30 min prior to insufflating cocaine increased both peak and area under the curve cocaine plasma levels from 140 to 240 ng/mL (Lukas et al., 1994), opposite in direction to our findings. The authors of that study linked the increases in cocaine plasma levels to the route of cocaine administration, speculating that cannabis-related vasodilation of the nasal mucosa may have counter-acted the vasoconstrictive effects of cocaine to increase its absorption. In our study, we hypothesized that we would find a similar impact of cannabis on cocaine plasma levels, despite differences in route of administration. Instead, we found that the cannabis pretreatment resulted in overall reductions, as opposed to increases, in cocaine and cocaine metabolite plasma levels. We cannot speculate as to the pharmacokinetic mechanisms contributing to the reductions in our study. In rodents, lower doses of THC (15 or 30 mg/kg, i.p.) pretreatment did not affect brain levels of cocaine (40 mg/kg, i.p.), but significantly higher brain cocaine levels were observed at a substantially higher THC dose (120 mg/kg, i.p.; (Reid and Bornheim, 2001).

In terms of subjective effects, we found that cannabis prior to cocaine administration modulated some cocaine responses, while cocaine did not alter the magnitude or quality of any of cannabis's effects. Relevant to co-use, inclusion of cannabis attenuated some effects of cocaine, including loss of appetite, while maintaining levels of reported calm otherwise reduced by cocaine during sessions. Additionally, tiredness increased while talkativeness was reduced by cannabis pretreatment. These findings contrast with prior studies. One study found that smoked cannabis (2.7 % THC) 13 min prior to intravenous cocaine (32 mg) increased cocaine's subjective effects, including the magnitude and duration of 'High' and 'Stimulated,' relative to cocaine alone (Foltin et al., 1993). A separate study found that

smoked cannabis (2.5 % THC) prior to insufflating cocaine (63 mg/70 kg) decreased the latency to detect cocaine's subjective effects, while increasing the duration of subjective ratings of cocaine-induced euphoria (Lukas et al., 1994). Together, the profile of subjective effects in our study indicate that cannabis pretreatment does not increase the positive subjective effects of cocaine, but rather, might attenuate some of cocaine's effects.

Cannabis and cocaine each produce elevations in heart rate when administered independently, (Foltin et al., 1995; Liu et al., 2018). However, findings from the few studies examining the co-administration of these two drugs have been mixed. One study found that cannabis (2.7 % THC) smoked 13 min prior to intravenous cocaine (32 mg) increased both the magnitude and duration of drug-induced tachycardia compared to administration of either drug alone (Foltin et al., 1987). In another study examining cardiovascular effects of insufflating cocaine (4–96 mg), the inclusion of cannabis (2.9 % THC) did not increase heart rate relative to cannabis alone (Foltin and Fischman, 1989). A third study found that cannabis (2.64 % THC) administered 30 min prior to insufflating cocaine (63 mg/70 kg) increased cocaine-induced tachycardia, however there was no cannabis-only condition to enable the assessment of potential additive effects (Lukas et al., 1994). In the current study, we found that cannabis and cocaine increased heart rate across the 0, 12, and 25 mg cocaine sessions as expected. However, our results do not suggest that these increases are greater than those seen with either drug alone.

How might pharmacodynamic factors play into our observed subjective and physiological effects and relate to previous studies? Although the impact of cannabis on the pharmacokinetics of cocaine might primarily account for the cannabis-related changes in cocaine's subjective and cardiovascular responses, it is important to consider the known pharmacodynamic interactions between these two drugs and their receptor targets. THC is a partial agonist of cannabinoid receptors (CB_1Rs), which, in the brain, act to inhibit the release of several neurotransmitters and neuromodulators, including dopamine (Piomelli, 2003, 2014), the neuromodulator well-known to mediate the subjective effects of cocaine (Ikegami and Duvauchelle, 2004). Although CB_1Rs are not expressed on dopaminergic axon terminals, they are densely expressed in brain nuclei that house dopamine cell bodies (Bloomfield et al., 2019). Within these nuclei, CB_1Rs are primarily expressed on interneurons that release GABA, an inhibitory neurotransmitter that regulates the activity of surrounding dopamine cells (Tsou et al., 1998). The presence of THC in the brain activates CB_1Rs to reduce GABA release and disinhibit dopamine cell activation, facilitating the release of dopamine throughout dopamine pathways in the brain (Araque et al., 2017; Augustin and Lovinger, 2018; Cheer et al., 2007; Wang and Lupica, 2014). From a pharmacodynamic perspective, pretreatment of cannabis prior to cocaine exposure might buffer the impact of additional dopaminergic-related activity associated with cocaine, especially at high doses of THC. Our study used a higher THC strength (5.6 % THC) than earlier reports (≤ 2.9 % THC), which might have contributed to the absence of THC-related increases in ratings such as 'Stimulated' reported in earlier studies (Foltin et al., 1993; Lukas et al., 1994). We also note that these studies occurred decades before our study, and differences related to cannabis use, including potency in cannabis products or cultural attitudes toward cannabis, may have influenced the results.

This study included both strengths and limitations. The major strength of the study was a systematic design that included two active cocaine doses in a previously untested drug combination, smoked cocaine with cannabis. The inpatient setting enabled control for acute and residual drug effects, while ensuring adequate sleep and food intake before testing. Our study was limited by a relatively small sample size, the inclusion of only males and mostly Black participants. These factors limit the generalizability of the findings. Additionally, the co-administration schedule included cannabis pretreatment but never cocaine pretreatment nor any co-administration at the same time. The testing schedule might also have influenced the pharmacodynamics and pharmacokinetics of the study drugs. Future studies may assess co-administration using a design that includes cocaine administration prior to cannabis, which may offer additional insight in a potentially more etiologically relevant model of co-use. That is, anecdotally, our participants suggested that cannabis was often used to end a cocaine-related binge, which was not modeled by the current study.

In conclusion, our examination of smoked cannabis (5.6 % THC) prior to smoked cocaine (12, 25 mg) found few interactions between the drugs, despite both drugs showing robust effects on their own. Although we found no evidence for enhanced cocaine effects after cannabis, we found evidence for reductions in some cocaine effects, including reductions in peak plasma levels of cocaine and reductions in cocaine's effect on appetite and reported calm. Future studies should explore additional doses of each drug, and in reverse order of administration, including whether the drug interactions impact cocaine's reinforcing effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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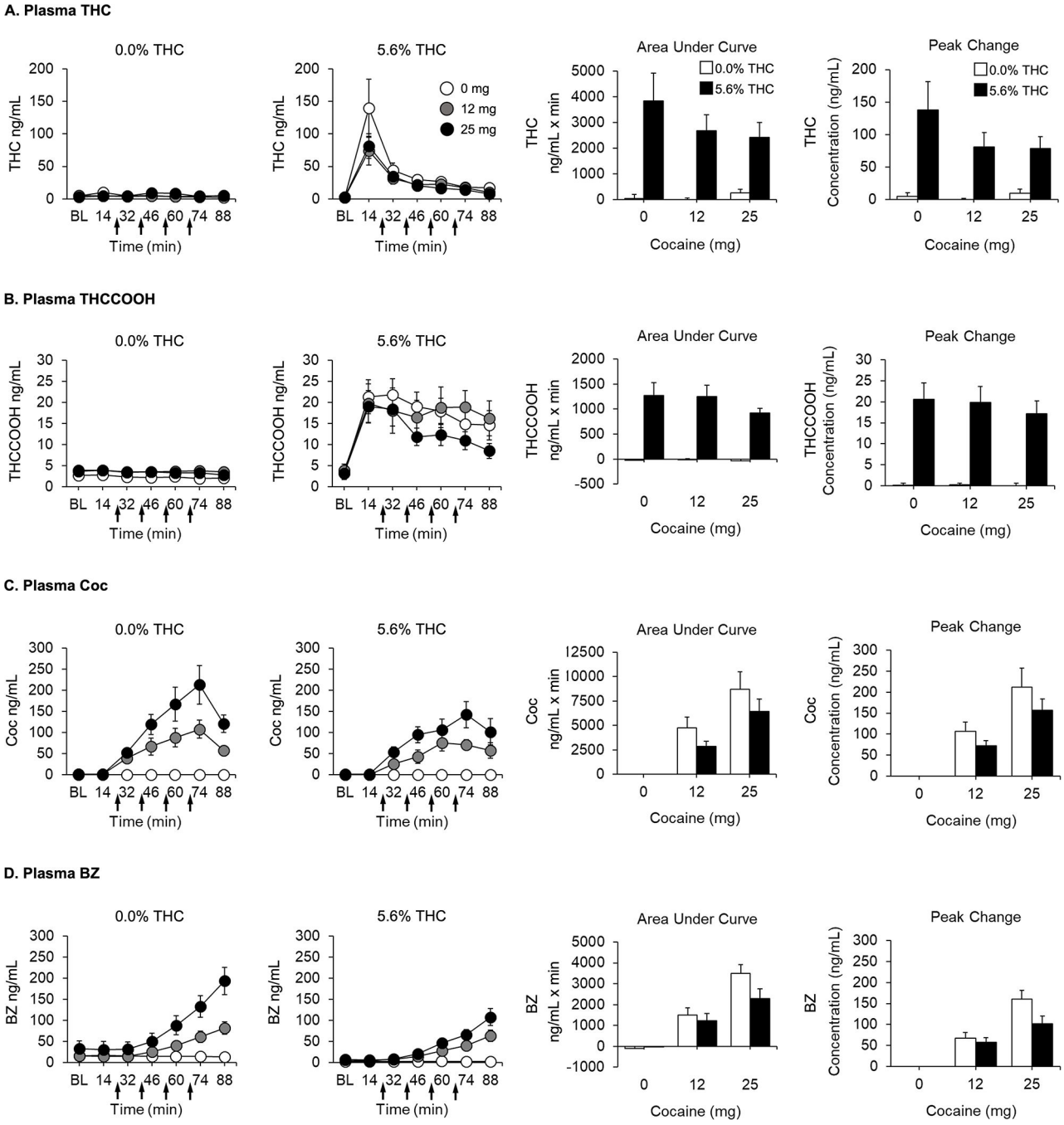

Fig. 1.

Plasma levels of THC, cocaine, and metabolites after co-administration of cannabis and cocaine. Area Under Curve and Peak Change plasma levels of Δ9-tetrahydrocannabinol (THC) (A) and metabolite 11-nor-9-carboxy-Δ9-THC (THCCOOH) (B) increased after active cannabis (5.6 % THC) relative to inactive cannabis (placebo; 0.0 % THC), but were unaffected by cocaine dose (0, 12, 25 mg) (repeated-measures ANOVA, main effects of cannabis, ps < 0.05). Area Under Curve and Peak Change plasma levels of cocaine (C) and metabolite benzoylecgonine (BZ) (D) dose-dependently increased after cocaine (12, 25

mg) (repeated-measures ANOVA, main effects of cocaine, ps < 0.05). Peak cocaine and BZ were significantly reduced by active cannabis (repeated-measures ANOVA, significant main effect of cannabis, $p < 0.05$). Area Under Curve BZ levels were also significantly reduced by active cannabis (repeated-measures ANOVA, significant cannabis and cocaine interaction, $p < 0.05$ and main effect of cannabis, $p < 0.05$). Data expressed as mean ± SEM. Arrows indicate cocaine administrations.

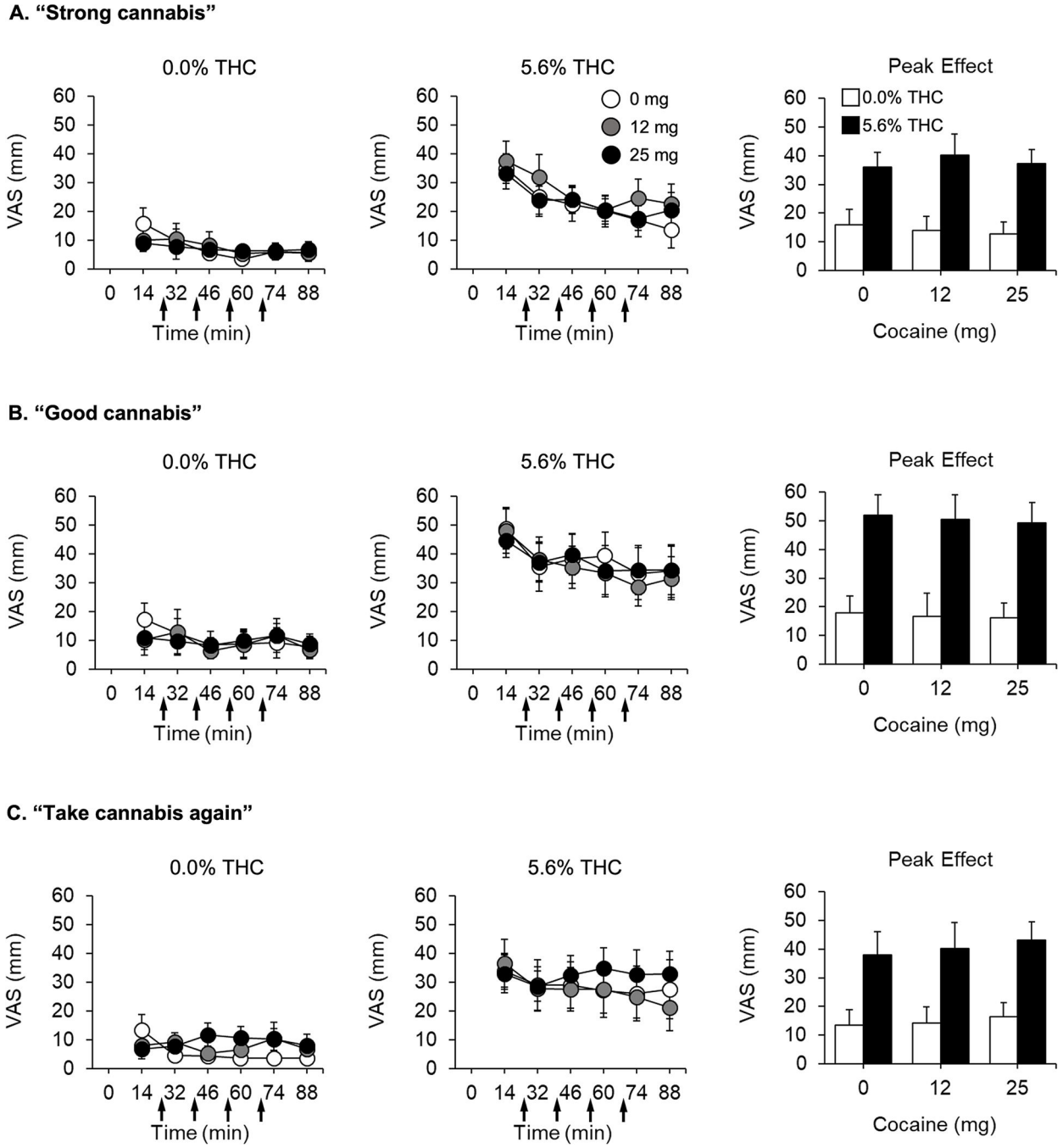

Fig. 2.

Cannabis Rating Form responses after co-administration of cannabis and cocaine. Active cannabis (5.6 % THC) increased peak ratings of cannabis strength, "Strong cannabis" (A), good cannabis effects, "Good cannabis" (B), and willingness to take the cannabis again, "Take cannabis again" (C), relative to inactive cannabis (placebo; 0.0 % THC). CRF responses were not affected by cocaine dose (0, 12, 25 mg) (repeated-measures ANOVA for each CRF item, main effects of cannabis, ps < 0.05). Peak Effect indicates that this measure

did not include a baseline from which a peak change score would be derived. Data expressed as mean ± SEM. Arrows indicate cocaine administrations.

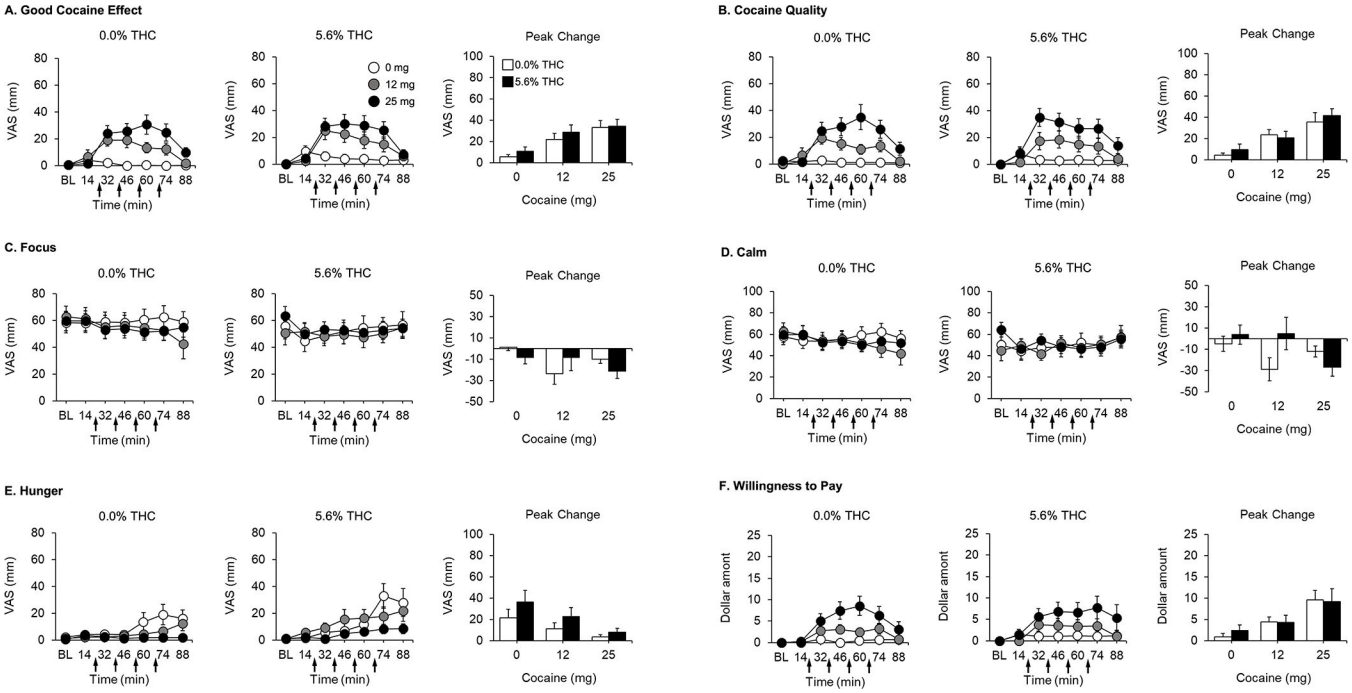

Fig. 3.

Visual analog scale responses after co-administration of cannabis and cocaine. Cocaine (12, 25 mg) dose-dependently increased peak ratings of Good Cocaine Effect (A), Cocaine Quality (B), and Willingness to Pay (up to $25) (F) (repeated-measures ANOVA for each VAS item, main effects of cocaine dose, ps < 0.05). Cocaine also dose-dependently reduced ratings of Focus (C), Calm (D), and Hunger (E), the latter of which was increased by active (5.6 % THC) relative to inactive (placebo; 0.0 % THC) cannabis (repeated-measures ANOVA for each VAS item, interactions not significant, main effects of cocaine dose, ps < 0.05; for Hunger, main effect of cannabis, $p < 0.05$). Data expressed as mean ± SEM. Arrows indicate cocaine administrations.

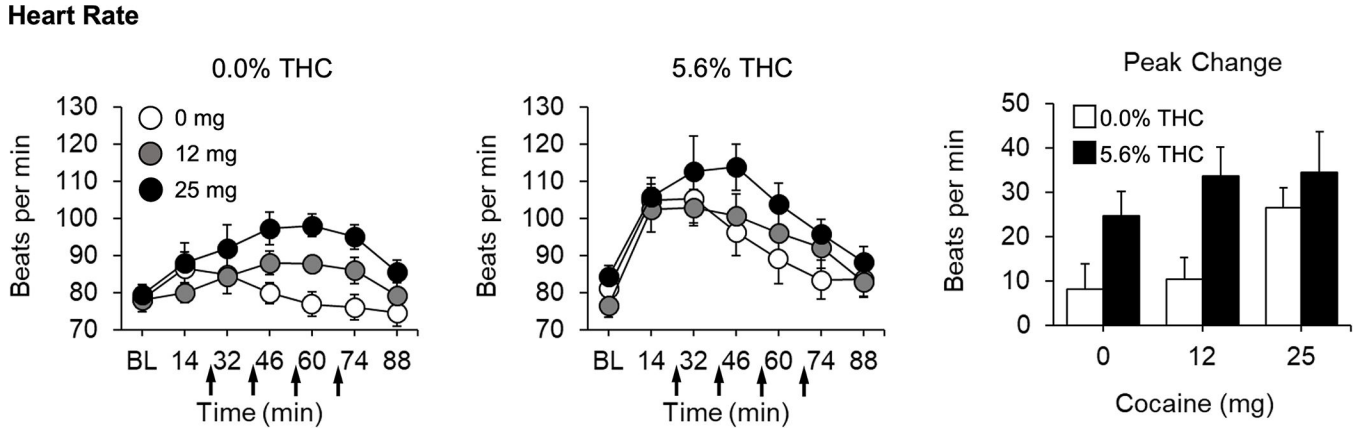

Fig. 4.

Heart rate after co-administration of cannabis and cocaine. Peak heart rate increased after active cannabis (5.6 % THC) relative to inactive cannabis (placebo; 0.0 % THC) (repeated-measures ANOVA, interaction not significant; main effect of cannabis, $p < 0.05$). Data expressed as mean ± SEM. Arrows indicate cocaine administrations.

Table 1

Demographics.

Category	*n* or Mean ± SD (Range)
Age, years 2	43.2 ± 6.1 (34–53)
BMI (kg/m^2)	28.8 ± 3.6 (22.7–33.5)
Race / Ethnicity	
Black or African American	8
Asian	1
Cannabis Use	
Age first used, years	18.6 ± 10.2 (12–43)
Days/week	2.3 ± 1.2 (1–4)
$/week	23.8 ± 16.9 (10–60)
Cocaine Use	
Age first used, years	21.1 ± 7.5 (14–34)
Days/week	4.6 ± 2.1 (1.5–7)
$/week	288.3 ± 218.5 (100–800)
Alcohol Use days/week	
Days/week	3.2 ± 2.0 (1–7)
Drinks/occasion	4.1 ± 2.4 (1–8.3)
Cigarettes/day	8.7 ± 5.1 (3–20)