Drug and Alcohol Dependence 167 (2016) 112–120

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Sex-dependent effects of cannabis-induced analgesia

Ziva D. Cooper*, Margaret Haney

Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA

ARTICLE INFO

Article history:
Received 14 January 2016
Received in revised form 28 July 2016
Accepted 1 August 2016
Available online 5 August 2016

Keywords:
Cannabinoids
Analgesia
Sex-differences
Abuse liability
Subjective effects

ABSTRACT

Background: Preclinical studies demonstrate that cannabinoid-mediated antinociceptive effects vary according to sex; it is unknown if these findings extend to humans.
Methods: This retrospective analysis compared the analgesic, subjective and physiological effects of active cannabis (3.56–5.60% THC) and inactive cannabis (0.00% THC) in male (N = 21) and female (N = 21) cannabis smokers under double-blind, placebo-controlled conditions. Pain response was measured using the Cold-Pressor Test (CPT). Participants immersed their hand in cold water (4 °C); times to report pain (pain sensitivity) and withdraw the hand (pain tolerance) were recorded. Subjective drug ratings were also measured.
Results: Among men, active cannabis significantly decreased pain sensitivity relative to inactive cannabis ($p < 0.01$). In women, active cannabis failed to decrease pain sensitivity relative to inactive. Active cannabis increased pain tolerance in both men women immediately after smoking ($p < 0.001$); a trend was observed for differences between men and women ($p < 0.10$). Active cannabis also increased subjective ratings of cannabis associated with abuse liability ('Take again,' 'Liking,' 'Good drug effect'), drug strength, and 'High' relative to inactive in both men and women ($p < 0.01$).
Conclusions: These results indicate that in cannabis smokers, men exhibit greater cannabis-induced analgesia relative to women. These sex-dependent differences are independent of cannabis-elicited subjective effects associated with abuse-liability, which were consistent between men and women. As such, sex-dependent differences in cannabis's analgesic effects are an important consideration that warrants further investigation when considering the potential therapeutic effects of cannabinoids for pain relief.

1. Introduction

Cannabis is the most widely used illicit drug worldwide (United Nations Office in Drugs and Crime, 2013) and has the highest rates of abuse in the United States relative to other illicit drugs, with 18.9 million people over the age of 12 reporting use in the previous month, a number that has increased by over 25% since 2007 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2012). While epidemiological reports consistently demonstrate that men use cannabis more frequently than women (Substance Abuse and Mental Health Services Administration, 2012), seek treatment for cannabis use more often than women (TEDS, 2012) and are at a higher risk for developing Cannabis Use Disorder (CUD; Stinson et al., 2006), a trend is emerging with a growing number of women reporting cannabis use for medical purposes (McConnell et al., 2014; Finseth et al., 2015; Ryan-Ibarra et al., 2015). Given this emerging trend, identifying potential sex-differences in the therapeutic effects and risks associated with cannabis is a public health imperative that has not yet been explored.

Although being male is a risk factor for developing CUD, women show an accelerated progression from first use to CUD relative to men, providing evidence for a 'telescoping effect' (Hernandez-Avila et al., 2004; Ehlers et al., 2010; Khan et al., 2013). Recent controlled studies in male and female cannabis users matched for current use demonstrated that while both men and women showed similar levels of intoxication following cannabis administration; women report higher ratings associated with abuse liability, such as liking the drug and willingness to take again (Cooper and Haney, 2014). The increased sensitivity observed in that clinical study corresponds to preclinical findings demonstrating that female laboratory animals are more sensitive to a range of behavioral and physiological effects of cannabinoids (for review, see Craft et al., 2013). Relative to male rats, females are more sensitive to the reinforcing effects of cannabinoids with faster acquisition

* Corresponding author.
E-mail addresses: zc2160@cumc.columbia.edu, cooperz@nyspi.columbia.edu (Z.D. Cooper).

http://dx.doi.org/10.1016/j.drugalcdep.2016.08.001
0376-8716/

of cannabinoid self-administration, higher rates of responding for cannabinoids (Fattore et al., 2007), and higher rates of cue and drug-induced reinstatement (Fattore et al., 2010). However, in addition to the increased susceptibility to the negative effects of cannabinoids, female rats are also more sensitive to cannabinoid-induced antinociception relative to males in both acute and chronic models of pain (Tseng and Craft, 2001; Craft et al., 2012, 2013). These preclinical findings suggest that while women may be more sensitive to the abuse-related effects of cannabis, cannabis may also be more effective as an analgesic in women relative to men; similar sex differences in analgesia have been shown with opioids (for review, see Campesi et al., 2012). Given that pain is one of the primary indications for which medical cannabis is used (Ilgen et al., 2013; Bonn-Miller et al., 2014), understanding if these preclinical findings translate to humans is critical to predicting clinical risks and outcomes associated with medical cannabis use in women, a growing population of users.

This retrospective analysis was designed to investigate if there are sex-dependent differences in cannabis' analgesic effects in humans. Apart from one study in healthy, non-cannabis using participants that identified nabilone-induced decreases in hyperalgesia in women but not men (Redmond et al., 2008), most studies of cannabinoid-induced analgesia have tested only one sex (Hill et al., 1974; Buggy et al., 2003; Greenwald and Stitzer, 2000; Kraft et al., 2008; Ellis et al., 2009; Lee et al., 2013) or have not included sex as a factor in the data analysis (Noyes et al., 1975; Karst et al., 2003; Naef et al., 2003; Svendsen et al., 2004; Abrams et al., 2007; Nurmikko et al., 2007; Rog et al., 2007; Wilsey et al., 2008, 2013; Ware et al., 2010; Issa et al., 2014; Wallace et al., 2007). We published a study designed to compare the dose-dependent analgesic effects of THC administered orally (dronabinol) versus smoked cannabis with delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, in 15 men and 15 women. Included in the overall analysis was an exploratory assessment of potential sex-dependent analgesia across all the doses; 10 and 20 mg dronabinol, 1.98 and 3.56% THC cannabis, and a placebo dronabinol and inactive cannabis (0.0% THC) condition. While this overall analysis did not yield significant differences in pain responses between men and women (Cooper et al., 2013), differences in the analgesic effects of cannabis between men and women emerged upon a more in-depth investigation of separate dose conditions. This retrospective analysis was designed to further examine sex-dependent effects of specifically cannabis-induced analgesia and draws from a larger pool of participants (N = 21 men and N = 21 women). Using double-blind, placebo-controlled methods, the analgesic effects of active cannabis was compared to inactive cannabis. Pain response was assessed using the Cold Pressor Test (CPT), a laboratory model of pain that has predictive validity for clinical efficacy of opioid analgesics in non-pain populations (Zacny et al., 1996a; Conley et al., 1997) and has been used to demonstrate the analgesic effects of smoked cannabis and oral THC (Cooper et al., 2013). In addition to analgesia, cannabis' subjective and cardiovascular effects in men and women were also compared to determine generalizability of cannabis' sex-dependent effects.

2. Methods

Data from two outpatient studies carried out at New York State Psychiatric Institute were used for this analysis (total N = 49). These double-blind, within-subject studies, designed to assess the analgesic effects of cannabinoids in non-treatment seeking, recreational (non-medical) cannabis smokers, measured the subjective ratings of drug quality, drug effect, mood, and physiological effects of a single strength of active cannabis (3.56–5.60% THC, active strength varied according to study) relative to inactive cannabis (0.00% THC). All participants were included from the first study (N = 15 women and 15 men; Cooper et al., 2013). For the second study (N = 6 women and 13 men), data from 6 men that best matched the women for frequency of cannabis use (days/week) and amount smoked per day (joints/day) were used. This matching was done to account for tolerance to cannabis' effects that occur with repeated use (Haney et al., 1997; Hart et al., 2002). Subjective and cardiovascular effects of cannabis smoked according to a controlled smoking procedure were analyzed according to cannabis condition (active and inactive) and sex for each endpoint.

2.1. Participants

Volunteers ages 21–50 were recruited through newspaper advertisements for a study on the effects of cannabis on pain response, mood, and physiology. Those who met inclusion/exclusion criteria after an initial telephone screen were invited to the laboratory for further screening. Prior to enrollment, participants gave written informed consent, received a psychiatric and medical evaluation, and provided a detailed drug use and medical history. All eligible participants currently smoked >3 cannabis cigarettes at least four times a week for the previous four weeks before screening, based on self-report and clinical interviews, and tested positive on a cannabis urine toxicology screen. Participants were accepted into the study if they were healthy, as determined by a physical examination, electrocardiogram, and urine and blood chemistries. Participants were excluded if they had current pain, repeatedly used other illicit drugs as determined by urine toxicology and self-report, or met criteria for alcohol dependence. Urine toxicology screens were performed during every screening visit and before each session. Exclusion criteria included Axis I psychopathology (DSM-IVth edition) as assessed by clinical interview, current use of over-the-counter or prescription medications, with the exception of oral contraceptives, pregnancy or nursing. Volunteers were told that during each session they would smoke a portion of a cannabis cigarette, but that the strength of the cannabis would vary. Participants were admitted into the studies only after written informed consent to participate was given and eligibility criteria were verified. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and were in accord with the Declaration of Helsinki.

2.2. Design and procedures

The studies included 5–8 outpatient sessions over the course of 2–8 weeks at the New York State Psychiatric Institute. Sessions began around 9 AM, and were 6–7 h in duration. Before study onset, participants were familiarized with computerized tasks, study procedures, and the CPT with 1 or 2 training sessions. Data obtained from 21 men and 21 women were used for the present analysis. Of these, 15 men and 15 women participated in a study investigating the analgesic effects of cannabis (0.00, 1.98, or 3.56% THC relative to dronabinol (Cooper et al., 2013) and 6 men and 6 women participated in a study assessing the effects of cannabis (0.00 or 5.60% THC) combined with an FDA-approved medication (findings not yet published). During each session, a capsule containing placebo or medication was administered followed by cannabis (active or inactive) smoking. A within-subject design was used for these two studies in which all participants received active and inactive cannabis and medication strengths; the order of drug conditions was randomized. For this analysis, data obtained from the placebo session (placebo oral medication and inactive cannabis) were compared to data obtained from the session when only active cannabis was administered (placebo oral medication and active cannabis); thus, results only reflect outcomes from the placebo medication sessions.