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Ventilatory-depressant effects of opioids alone and in combination with cannabinoids in rhesus monkeys

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Abstract

Pain is a serious health problem that is commonly treated with opioids, although the doses of opioids needed to treat pain are often similar to those that decrease respiration. Combining opioids with drugs that relieve pain through non-opioid mechanisms can decrease the doses of opioids needed for analgesia, resulting in an improved therapeutic window, but only if the doses of opioids that decrease respiration are not similarly decreased. Using small doses of opioids to treat pain has the potential to reduce the number of overdoses and deaths. This study investigated whether the cannabinoid receptor agonists ⁹-tetrahydrocannabinol (⁹-THC) and CP 55,940 modify the ventilatory-depressant effects of morphine and fentanyl in three monkeys. Ventilatory parameters, including minute volume (V_E), were monitored with a head plethysmograph. When given alone, morphine (0.032 – 10 mg/kg) and fentanyl (0.00032 – 0.1 mg/kg) dose dependently decreased V_E . Doses of ⁹-THC (1 mg/kg) and CP 55,940 (0.01 mg/kg) that enhance the potency of opioids to produce antinociception, alone modestly decreased ventilation but did not significantly change morphine or fentanyl dose-effect curves. A larger dose of CP 55,940 (0.032 mg/kg) shifted the fentanyl dose-effect curve downward in two monkeys, without significantly changing the morphine dose-effect curve. In summary, cannabinoid receptor agonists, which increase the potency of opioids to produce antinociception, did not increase their potency to depress ventilation. Thus, the therapeutic window is greater for opioids when they are combined with cannabinoid receptor agonists, indicating a possible advantage for these drug mixtures in treating pain.

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Keywords

mu opioid receptor agonist; cannabinoid receptor agonist; rhesus monkey; ventilation; respiration; drug-drug interactions

1. Introduction

Since the 1990's, opioids have been prescribed more often and in greater quantities than ever before which has contributed to a marked rise in drug overdose deaths (Centers for Disease Control and Prevention, 2011; Compton and Volkow, 2006; Rudd et al., 2016). Increased overdose from opioids is due, in part, to the narrow therapeutic window of this drug class; doses of *mu* opioid receptor agonists that are necessary to treat pain are often only slightly smaller than, and in some cases the same as, doses that decrease respiration, the fatal effect of most opioids (Dunn et al., 2011; France et al., 1992; Gerak et al., 1994). One strategy to increase the therapeutic window of opioids is to combine opioids with other drugs that also have analgesic properties but act through non-opioid mechanisms, which should reduce the dose of opioid needed to relieve pain without altering the dose that decreases respiration (Volkow and McLellan, 2016). Cannabinoid receptor agonists, such as the psychoactive constituent of marijuana Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and the synthetic cannabinoid receptor agonist (–)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (CP 55,940), have antinociceptive effects (Pertwee, 2001; Walker and Hohmann, 2005) and have been used to treat pain in humans (Hosking and Zajicek, 2008; Ware, 2010). When combined with opioids in nonhuman primates, ineffective doses of cannabinoid receptor agonists increased the potency of *mu* opioid receptor agonists to produce antinociceptive effects in a warm-water tail withdrawal procedure (Li et al., 2008; Maguire et al., 2013; Maguire and France, 2014); such combinations will be beneficial for treating pain only if the potency of opioids to produce other effects, like respiratory depression, is not similarly increased.

In humans and other species, *mu* opioid receptor agonists markedly depress respiration and pulmonary ventilation as evidenced by dose-dependent decreases in minute volume (V_E) in nonhuman primates breathing air or 5% CO₂ in air (Gerak et al., 1998; Vivian et al., 1998). The effects of cannabinoid receptor agonists on respiration appear to be less pronounced, compared with opioids, and might vary among species (Padley et al., 2003; Pfitzer et al., 2004; Schmid et al., 2003; Vivian et al., 1998; Malit et al., 1975; Mathew et al., 1992). Interactions between opioids and cannabinoids have not been extensively studied. In healthy adult volunteers, combinations of Δ^9 -THC and morphine decreased respiratory rate in some subjects (Naef et al., 2003) and oxymorphone enhanced the ventilatory-depressant effects of Δ^9 -THC (Johnstone et al., 1975), although these studies were limited in that either a single dose combination was studied or very large doses of Δ^9 -THC were used, respectively.

The purpose of the current study was to examine whether cannabinoid receptor agonists modify the ventilatory-depressant effects of opioids. This study extends a growing literature on interactions between opioids and cannabinoids in nonhuman primates using a variety of highly translatable procedures. Previous studies reported that the antinociceptive potency of

opioid/cannabinoid mixtures depended on the pharmacological efficacy of both constituents of the mixture (i.e., Maguire and France, 2014). To test whether pharmacological efficacy also influences effects on ventilation, two cannabinoid receptor agonists with different efficacies were studied in combination with each of two *mu* opioid receptor agonists with different efficacies.

2. Material and methods

2.1 Subjects

Three adult rhesus monkeys (2 female, ME and OL; 1 male, GI) weighing between 6 and 10 kg were used for the study. All subjects had previously received opioids and cannabinoids. Body weights were maintained by daily feeding of high-protein chow (High Protein Monkey Diet, Harlan Teklad, Madison, WI, USA) along with fresh fruit and peanuts. Water was continuously available in home cages. Subjects were individually housed under a 14h/10h light/dark cycle. Animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and the *2011 Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, USA).

2.2 Apparatus

During experiments subjects were seated in commercially available chairs (model R001; Primate Products, Miami, FL, USA). A helmet (Plas-Labs, Lansing, MI, USA) was placed over the head of the monkey and rested on a Lexan plate. A latex neck dam separated the helmet from the Lexan plate and prevented the escape of air. A large animal bias flow supply (Data Sciences International, St. Paul, MN, USA) drew air into the helmet at a flow rate of 10 l/min using an air flow meter (model 4140F, TSI Inc., Shoreview, MN, USA). Pressure changes in the helmet were measured by a pneumotachometer; the analog signal was transformed to digital using a carrier signal conditioner card connected to an acquisition module (Model ACQ-770, Data Sciences International), and a computer running Ponemah software (version 4.01; Data Sciences International) converted the pressure changes to respiratory rate (f) and tidal volume (V_T). Minute volume (V_E) was the product of f and V_T . An experimenter monitored subjects continuously.

2.3 Procedure

During the first 10 min of each session, parameters for pulmonary ventilation were recorded in the absence of drug, and test sessions were subsequently conducted in that subject as long as the mean V_E for the last 3 min of that 10-min period was within 1 standard deviation of the control mean V_E , which was determined by averaging the last 3 min of each 15-min period during 4 sessions in which no drug was administered. The first injection, which was either vehicle, 9 -THC, or CP 55,940, occurred at the end of the 10-min period. Monkeys were not disturbed and ventilatory parameters were measured for the next 60 min; this interval between administration of a cannabinoid receptor agonist and determination of a dose-effect curve for an opioid receptor agonist was used previously to demonstrate increased potency of opioids in a warm-water tail withdrawal procedure in monkeys (Li et

al., 2008; Maguire et al., 2013; Maguire and France, 2014). Thereafter, monkeys received an injection every 15 or 30 min. For some sessions, sham injections were given every 15 min, and these sessions lasted for 3 h. For other sessions, dose-effect curves for morphine and fentanyl were determined using a cumulative dosing procedure. Doses of opioids ranged from an ineffective dose, which did not alter V_E as compared to the control mean, to one that decreased V_E below 65% of the control mean. Morphine was given every 30 min whereas fentanyl was given every 15 min based on previous studies (Gerak et al. 1998).

2.4 Drugs

Morphine sulfate and fentanyl hydrochloride (Drug Supply Program, National Institute on Drug Abuse, Rockville, MD, USA) were dissolved in sterile water. 9 -THC (Drug Supply Program, National Institute on Drug Abuse) was provided in a solution of 100 mg/ml in ethanol and diluted with a vehicle containing 1 part ethanol, 1 part emulphor and 18 parts saline. CP 55,940 ((-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol; Sigma-Aldrich, St. Louis, MO, USA) was dissolved in the vehicle containing 1:1:18 ethanol:emulphor:saline. All drugs were administered subcutaneously.

2.5 Data Analyses

Data were collected every minute throughout the session and transformed to respiration rate (inspirations/min, f) and tidal volume (ml/inspiration, V_T); minute volume (ml/min, V_E) was the product of f and V_T . When changes in ventilatory parameters were monitored over time, data were averaged across the 10 min that preceded each sham injection as well as the 10 min at the end of the session and plotted as a function of time since administration of vehicle or a cannabinoid receptor agonist; when dose-effect curves were determined for an opioid, data were averaged across the last 10 min of each dosing condition and plotted as a function of opioid dose.

Control values for V_E , V_T , and f were calculated from 4 sessions that lasted 3 h and during which only saline or sham injections were given. For each session, the last 10 min of each 15-min cycle, beginning 60 min after the initial vehicle injection, were averaged, and then the mean for each session was averaged (+ S.E.M.) across the 4 sessions. In order to determine whether V_E , V_T , or f varied during the session, one-way ANOVA was performed on the cycles comprising min 70 through 160 of the 4 control sessions; the factor was time.

For each cannabinoid receptor agonist, effects on V_E over time were compared using repeated measures two-way ANOVA; cannabinoid dose (or vehicle) was one factor and time since injection was the second factor. For monkeys ME and OL, vehicle was compared to 1 mg/kg 9 -THC in one analysis, and vehicle, 0.01 mg/kg CP 55,940, and 0.032 mg/kg CP 55,940 were compared in another. For monkey GI, vehicle, 0.32 mg/kg 9 -THC, and 1 mg/kg 9 -THC were compared in one analysis, and vehicle was compared to 0.01 mg/kg CP 55,940 in another. Each condition was determined twice; V_E was first averaged across the last 10 min of each time period and then averaged across determinations. Similarly, the effects of each cannabinoid receptor agonist on the ventilatory-depressant effects of morphine or fentanyl were analyzed using repeated measures two-way ANOVA with

cannabinoid dose (or vehicle) as one factor and opioid dose as the other factor. For instances in which the largest dose of the opioid was not studied under all conditions (ME and GI: 10 mg/kg morphine and 0.1 mg/kg fentanyl), the largest dose was excluded from analyses.

In all instances in which a significant effect was obtained, post-hoc analyses were performed using the Holm-Sidak method. Data analyses were performed using GraphPad Prism (version 6.07, GraphPad, La Jolla, CA, USA). An effect was considered significant when $P < 0.05$.

3. Results

The control mean (± 1 S.E.M.) V_E was 1608 ± 34 , 1613 ± 20 , and 1881 ± 16 ml/min for subjects ME, OL, and GI, respectively; the control mean (± 1 S.E.M.) V_T was 66.8 ± 0.7 , 57.4 ± 0.8 , and 68.7 ± 0.4 ml/inspiration for subjects ME, OL, and GI, respectively; and the control mean (± 1 S.E.M.) f was 24.0 ± 0.4 , 28.1 ± 0.2 , and 27.3 ± 0.1 for subjects ME, OL, and GI, respectively. Throughout the duration of this study, there was no significant change for individual subjects in V_E , V_T , or f across time during sessions in which drug was not administered (not shown).

When the effects of 1 mg/kg 9 -THC on V_E were compared with vehicle over time (Fig. 1), there was a significant interaction between time and pretreatment ($F [6,6] = 5.52$, $P = 0.028$) for monkey ME, and a significant effect of time ($F [6,6] = 4.86$, $P = 0.038$) for monkey OL. *Post-hoc* comparisons revealed that, by the end of the session (i.e., 150 min after injection), V_E had decreased significantly for ME (as compared with 60 and 75 min) and for OL (as compared with 75 and 90 min). Neither dose of 9 -THC (0.32 mg/kg and 1 mg/kg) significantly decreased V_E in monkey GI, as indicated by no main effect of cannabinoid pretreatment or time; the interaction between factors approached but did not reach statistical significance ($F [12,12] = 2.48$, $P = 0.07$). In contrast, 0.01 mg/kg CP 55,940 did not significantly alter ventilation in any monkey, compared with sessions in which drug was not administered, nor did the effect change over time, as indicated by no main effect of cannabinoid pretreatment or time and no interaction between factors. A larger dose of CP 55,940 (0.032 mg/kg) was studied once in monkey GI and decreased V_E ; this dose of CP 55,940 did not significantly decrease V_E in ME or OL.

Morphine dose dependently decreased V_E in all subjects, although the potency of morphine varied across monkeys (open circles, Fig. 2). When 1 mg/kg 9 -THC was administered 60 min before the first dose of morphine, there was no significant change in morphine dose-effect curves for monkeys ME and OL (upper left and center panels, Fig. 2). Two-way ANOVA indicated that there was a main effect of morphine dose (ME: $F [3,3] = 95.9$, $P = 0.0018$; OL: $F [4,4] = 46.5$, $P = 0.0013$) with no effect of 9 -THC pretreatment and no interaction. For monkey GI, pretreatment with 0.32 mg/kg 9 -THC did not significantly change the morphine dose-effect curve, as indicated by no main effect of morphine dose or 9 -THC pretreatment and no significant interaction (upper right panel, Fig. 2). Neither dose of CP 55,940 significantly changed the ventilatory-depressant effects of morphine in ME [main effect of morphine dose ($F [3,3] = 21.8$, $P = 0.0056$)] or OL [main effect of morphine dose ($F [4,4] = 260.8$, $P < 0.0001$)] as indicated by no main effect of CP 55,940 pretreatment

and no interaction (lower left and center panels, Fig. 2). For monkey GI, 0.01 mg/kg CP 55,940 modestly decreased V_E regardless of the dose of morphine (lower right panel, Fig. 2). There was a main effect of morphine dose ($F [3,3] = 13.3$, $p = 0.031$) and no significant main effect of CP 55,940 pretreatment or interaction between morphine dose and CP 55,940 pretreatment. Because 0.032 mg/kg CP 55,940 markedly decreased V_E in monkey GI, that dose was not studied with morphine (see Fig. 1).

Fentanyl also decreased V_E in a dose-dependent manner in all subjects (open squares, Fig. 3). Similar to morphine, the potency of fentanyl to decrease V_E varied across monkeys. When 1 mg/kg 9 -THC was administered before fentanyl, there was a main effect of fentanyl dose for monkeys ME and OL ($F [5,5] = 9.051$, $P = 0.0152$; $F [5,5] = 7.725$, $P = 0.0213$, respectively) with no main effect of 9 -THC pretreatment and no interaction. For monkey GI there was no main effect of fentanyl dose or pretreatment with 1 mg/kg 9 -THC, but there was a significant interaction ($F [5,5] = 5.177$, $P = 0.0477$). *Post-hoc* analyses indicated that 1 mg/kg 9 -THC significantly decreased V_E for doses of 0.32 and 10 μ g/kg fentanyl.

Similarly, neither dose of CP 55,940 significantly changed the fentanyl dose-effect curve for monkeys ME or OL. For both monkeys there was a main effect of fentanyl dose ($F [5,5] = 11.83$, $P = 0.0084$; $F [5,5] = 26.52$, $P = 0.0013$, respectively) with no main effect of CP 55,940 pretreatment and no interaction. For monkey GI there was no main effect of fentanyl dose or CP 55,940 pretreatment and no interaction.

4. Discussion

4.1

Mixtures of opioid receptor agonists and cannabinoid receptor agonists are being considered for the treatment of pain, in part, because cannabinoids enhance the antinociceptive effects of opioids in both preclinical (Cichewicz and Welch, 2003; Fischer et al., 2010; Li et al., 2008; Maguire and France, 2014) and clinical (Hosking and Zajicek, 2008; Naef et al., 2003) settings. Less well studied, although of considerable importance, is whether cannabinoids modify other effects of opioids, particularly adverse effects such as respiratory depression. The current study demonstrated that, at doses that enhance the potency of opioids for producing antinociception (Maguire et al., 2013; Maguire and France, 2014), cannabinoid receptor agonists have little or only modest effects on ventilation alone and do not alter the ventilatory-depressant effects of μ opioid receptor agonists. This relationship was observed with two drugs from each drug class. Even when an opioid was combined with a dose of cannabinoid that decreased ventilation on its own, the dose-effect curve for the opioid was not shifted leftward (e.g., monkeys ME and GI for 0.032 mg/kg CP 55,940 prior to fentanyl). Doses of μ opioid receptor agonists that decrease respiration and pulmonary ventilation are close to or the same as doses that produce antinociceptive effects on their own. For example, in rhesus monkeys, 10 mg/kg morphine produces 100% of the maximum possible effect in a warm-water tail withdrawal procedure (Li et al., 2008; Maguire and France, 2014) and decreases V_E to less than 70% of control in monkeys breathing air (current study) or 5% CO_2 (Gerak et al., 1998). However, doses of 9 -THC that alone are without significant effect in both assays, increase the potency of morphine to produce

antinociception (Maguire et al 2013) without altering its potency to decrease ventilation (current study). Taken together, these findings demonstrate that, although large doses of cannabinoid receptor agonists can decrease ventilation on their own, combining cannabinoids with opioids does not appear to increase the risk of overdose (and death due to respiratory depression), suggesting that a mixture might have a larger therapeutic window compared with an opioid alone.

The doses of the cannabinoids used in the current study were the same as those that increase the potency of opioids to produce antinociception (Maguire and France, 2014), and these doses of cannabinoids had varying effects of pulmonary ventilation, both within and between subjects. The variability in ventilatory-depressant effects of cannabinoid receptor agonists in rhesus monkeys is consistent with results from clinical reports, with some studies indicating that cannabinoids decrease respiration (Johnstone et al., 1975; Malit et al., 1975; Naef et al., 2003) and others reporting no effect (Mathew et al., 1992; Zwillich et al., 1978). The current study was not designed to comprehensively examine the ventilatory-depressant effects of Δ^9 -THC or CP 55,940 with only two doses of each drug being tested, based on previous studies in monkeys (Maguire and France, 2014). The potency of cannabinoid receptor agonists to decrease ventilation differed between subjects, with Δ^9 -THC and CP 55,940 being more potent in monkey GI than monkeys ME or OL. Indeed, a previous study reported that Δ^9 -THC and the cannabinoid receptor agonist WIN 55,212-2 dose-dependently decreased ventilation in rhesus monkeys breathing air or 5% CO₂ in air, with 1 mg/kg Δ^9 -THC decreasing V_E to 60% of control (Vivian et al., 1998). Thus, while cannabinoid receptor agonists alone can depress ventilation under some conditions, these effects are limited compared with the marked respiratory-depressant effects of opioids. That cannabinoids do not alter the ventilatory-depressant effects of opioids supports the increased safety of these drug mixtures, compared with opioids alone, for treating pain.

The current study was designed to measure pulmonary ventilation. Respiration is a complex process that involves the transport of air into and out of the lungs as well as the absorption of O₂ and removal of CO₂ from cardiovascular blood flow, and several methods have been used to assess respiration (for reviews see Jennet, 1968 and Keats, 1985). As such, the current findings describe one aspect of respiration, namely, the movement of air into the lungs as described by minute volume (V_E). This is an important distinction to make as drugs can affect different measures of respiration at doses that do not alter ventilation; however, the doses of opioids or cannabinoids used in the current study alter ventilation and overall respiration similarly (Borison, 1977; Gerak et al., 1998; Padley et al., 2003; Schmid et al., 2003; Vivian et al., 1998). For example, morphine was equipotent at decreasing V_E in monkeys breathing normal air and 5% CO₂ in air (Gerak et al., 1998), and CP 55,940 decreased f at doses that increased arterial pCO₂ in rats (Schmid et al., 2003). While the current study might be underestimating the interactions between μ opioid receptor agonists and cannabinoid receptor agonists on respiratory depression, it is plausible that ventilation and respiration are similarly affected by opioids and cannabinoids.

Given that opioids are commonly used to treat chronic pain, one important question that is not addressed by the current study is whether the ventilatory-depressant effects of opioid/cannabinoid mixtures are changed during daily treatment. In nonhuman primates, tolerance

and cross-tolerance develop between the antinociceptive effects of opioids and cannabinoids during daily treatment with morphine alone or in combination with 9 -THC (Gerak et al., 2015; Gerak and France, 2016). In contrast, daily administration of an opioid and a cannabinoid in rodents decreased the development of tolerance to the antinociceptive effects of the opioid (Cichewicz and Welch, 2003; Fischer et al., 2010; Smith et al., 2007). As differential tolerance has been noted between analgesic, euphoric, and respiratory effects of opioids (see White and Irvine, 1999, for review), any changes to tolerance that occur with opioid/cannabinoid mixtures might change overdose risk during repeated use, and additional studies are needed to determine whether the ventilatory-depressant effects of opioid/cannabinoid mixtures are altered during repeated treatment.

4.2

In conclusion, the ventilatory-depressant effects of the μ opioid receptor agonists morphine and fentanyl, at doses producing antinociceptive effects in a warm-water tail withdrawal assay (Gerak et al., 2015; Gerak and France, 2016; Maguire and France, 2014), were not enhanced by pretreatment with the cannabinoid receptor agonists 9 -THC or CP 55,940. Cannabinoid receptor agonists do not enhance other adverse effects of opioids. For example, in monkeys the discriminative stimulus effects of morphine and reinforcing effects of heroin were either not changed or attenuated by 9 -THC (Li et al., 2008; Li et al., 2012; Maguire et al., 2013). Overall, these results provide strong support for the notion that cannabinoid receptor agonists selectively increase the potency of opioids only for producing antinociception. Using small doses of opioids to treat pain, even in a mixture with a cannabinoid, will reduce the likelihood of incurring adverse effects, including respiratory depression. These promising findings indicate that mixtures might have a greater therapeutic window than opioids alone.

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Fig. 1.

Ventilatory effects (minute volume; V_E) of saline and cannabinoid receptor agonists (Δ^9 -THC or CP 55,940) beginning 60 min after injection for subjects ME (left), OL (middle), and GI (right). Unfilled diamonds and error bars represent the average and range of two control sessions that occurred near the time when tests with cannabinoids occurred. Filled circles and squares represent sessions in which Δ^9 -THC or CP 55,940 was administered, respectively. Abscissae represent the time since injection in min and ordinates represent minute volume (V_E) in ml/min.

Fig. 2.

Ventilatory effects of morphine 60 min after an injection of saline or a dose of Δ^9 -THC or CP 55,940 for subjects ME (left), OL (middle) and GI (right). Upper panels show data following injection of Δ^9 -THC while lower panels show data following injection of CP 55,940. Unfilled circles represent the effects of morphine after saline, filled circles represent the effects of morphine after Δ^9 -THC, and filled squares represent the effects of morphine after CP 55,940. Data points and error bars represent the mean and range of two determinations. The number “1” next to a data point indicates that dose combination was tested only once. Abscissae represent the dose of morphine in mg/kg and ordinates represent V_E in ml/min.

Fig. 3.

Ventilatory effects of fentanyl 60 min after an injection of saline or a dose of Δ^9 -THC or CP 55,940 for subjects ME (left), OL (middle) and GI (right). Upper panels show data following injection of Δ^9 -THC while lower panels show data following injection of CP 55,940.

Unfilled squares represent the effects of fentanyl after saline, filled circles represent the effects of fentanyl after Δ^9 -THC, and filled squares represent the effects of fentanyl after CP 55,940. Numbers in italics next to a data point indicate the value of V_E for that dose. Data points and error bars represent the mean and range of two determinations. The number "1" next to a data point indicates that dose combination was tested only once. Abscissae represent the dose of fentanyl in μ g/kg and ordinate represent V_E in ml/min.