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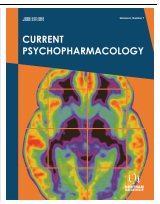

Intramuscular Route of Administration Increases Potency in Eliciting Cocaine-Induced Behavioral Sensitization

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Abstract: ***Background:*** Cocaine is the number one abused psychostimulant drug that reaches addiction criterion in the US. In animals, repeated administration of cocaine results in behavioral sensitization which is thought to represent adaptations in the mesolimbic dopamine neural circuitry, the reward pathway. Cocaine-induced behavioral sensitization is evident in rodents and quail when cocaine is administered intraperitoneally (IP).

Objective: The purpose of the current study was to investigate dose-dependent and temporal effects of acute and chronic intramuscular (IM) administration of cocaine in male quail.

Method: After habituation to the test chambers, male quail received an IM injection of saline, 3 or 10 mg/kg cocaine and were immediately placed in the chambers. Distance traveled (in meters) was recorded in 5 min time bins for 30 min. Testing was conducted once per day for ten days with each subject receiving the same treatment throughout the experiment. Other behaviors including pecking, preening, and feather fluffing were measured.

Results: Cocaine-induced behavioral sensitization and tolerance were evident at relatively low doses of IM cocaine. Dose-dependent effects were evident. IM cocaine also reduced feather fluffing, a behavior that typically occurs during hypothermia.

Conclusion: The findings replicated and extended previous research with pigeons and suggested that IM administration of cocaine may be a relatively potent route of administration. Potency of drugs of abuse may be related to the bioavailability of a drug and its addictive properties. Thus, studying drugs of abuse using an IM route of administration may be useful in drug addiction research.

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1. INTRODUCTION

Despite awareness of the harmful effects of cocaine taking, cocaine addiction persists. Cocaine is the number one abused psychostimulant drug that reaches addiction criterion in the US [1]. In animals, repeated administration of cocaine results in heightened motor stimulant effects, known as behavioral sensitization [2, 3]. Cocaine-induced sensitization is thought to represent adaptations in the mesolimbic dopamine neural circuitry, the pathway associated with reward [3]. These adaptations in the reward neural circuitry may later promote relapse [4].

In preclinical studies, the majority of cocaine sensitization studies utilize intraperitoneal (IP) injections as the primary route of administration in rodents [5-8] and quail [9-12]. Similar to rodent models, previous research in quail replicates the findings that IP administration of chronic cocaine

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dose-dependently enhances locomotor activity and induces cocaine sensitization [10, 11]. Specifically, cocaine sensitization is evident with IP administration of cocaine ranging from doses of 10 to 23 mg/kg in both rodents and quail using similar procedures [11, 13-15]. However, some studies show that IP injections of substances might have an estimated 23% miss rate and instead enter the kidney, small bowel, and intravascular system [16, 17].

There are differences in metabolism of drugs using IP versus IM routes of administration. IP administration undergoes the first-pass metabolism, which reduces the bioavailability of the drug [18]. However, IM injections avoid much of the first-pass metabolism, with 50-70% lower doses than IP while providing a similar plasma concentration [18, 19]. These differences in metabolism result in differences in cocaine's bioavailability [20, 21] which may, in turn, result in differences in potency of cocaine to induce sensitization.

IM administration of cocaine has been previously conducted in pigeons [22]. In this study, pigeons were given daily IM injections of 1, 3, and 10 mg/kg cocaine and locomotor activity, pecking, and preening were measured. A weighted-floor system was used in which locomotor activity was counted when the weight of a pigeon activated a switch on a particular floor section. All of the subjects received each dose in a within-subjects design. The results showed that all of the doses induced cocaine sensitization and cocaine dose-dependently decreased preening. Of particular interest, cocaine sensitization occurred at much lower doses (1 and 3 mg/kg) in pigeons using the IM route of administration compared to rodents and quail given IP administration of cocaine [9-11, 23-27].

In human drug addiction, cues in the environment may become associated with drug taking and later, in the absence of the drug, cause craving and subsequent relapse. Therefore, an animal model that is more visually-oriented may be of additional relevance to human drug addiction. Although rodents are the most common species used in drug addiction research, they typically do not have good visual acuity and tend to rely on multimodal cues in their environment. Japanese quail have color vision and high visual acuity [28] that is similar to humans. Therefore, they may be ideal subjects to study drug addiction phenomena that involve visual environmental cues.

The purpose of the current study was to determine the effect of IM administration of cocaine on drug-induced locomotor activity in male Japanese quail. To extend previous work [22], locomotor activity was assessed as distance traveled and a between-subjects design was used to examine group effects. The studies also measured time bins to determine more specific effects of acute and chronic IM cocaine.

2. METHODS

2.1. Subjects

Twenty-four (N = 24) adult male Japanese quail (*Coturnix japonica*) were supplied as eggs from Northwest Gamebirds (Kennewick, WA). Quail were hatched and raised in mixed sex groups until approximately four weeks of age, then housed in individual wire mesh cages (supplied by GQF Manufacturing, Savannah, GA). Male quail were randomly selected at 6-8 weeks old and maintained on a 19:8 hr light/dark cycle. Quail were maintained at 85% body mass, where food was available from 10 AM to 6 PM daily. This closely matches previously defined avian measures [29-31].

All experimental procedures were conducted according to the guidelines of the Institutional Animal Care and Use Committee (IACUC) at the University of Kentucky and thereby in accordance with the standards set forth by the 8th edition of the Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Bethesda, MD) was dissolved in physiological saline (0.9%) and injected intramuscularly (IM) at a volume of 1-ml/kg body weight. Doses of 3 mg/kg and 10 mg/kg and were chosen based on previous research that demonstrated cocaine-enhanced locomotor activity in pigeons with IM injections [22] and quail with IP injections [10, 11], respectively.

2.3. Apparatus

Distance traveled was used as an index of locomotor activity, and measured in 8 identical open field chambers. Each chamber had white plastic walls, screen mesh ceilings, and white corrugated paper the floor. The chambers measured 45.72 cm

tall and 55.88 cm in diameter. Distance traveled was collected using ANY-Maze video tracking software (San Diego Instruments, San Diego, CA). All trials were recorded and later analyzed for behavioral measures including pecking, preening, and feather fluffing. Behavioral measures, except for feather fluffing, were chosen based on previous literature [22].

2.4. Procedure

Male quail were randomly assigned to receive 3 mg/kg cocaine (n = 8), 10 mg/kg cocaine (n = 7), or saline (n = 8). Subjects were habituated to their assigned chamber for 30 min for two days before the start of the experiment. During testing, birds were weighed each day, injected IM with saline, 3 or 10 mg/kg cocaine and immediately placed in the chambers. Distance traveled (m) was recorded in 5 min time bins for 30 min. Testing was conducted once per day for ten days with each subject receiving the same treatment throughout the experiment. All trials were videotaped. White noise was used throughout each phase of the experiment to attenuate extraneous noise.

2.5. Statistical Analysis

Cocaine-induced behavioral sensitization was assessed by comparing distance traveled on day 1 to day 10 [32]. A repeated-measures analysis of variance (ANOVA) was performed on the day (1 and 10) as a repeated measure and treatment (saline, 3 and 10 mg/kg cocaine) as the between-subjects variable. To further probe a significant interaction, independent ANOVAs were conducted where appropriate.

Repeated-measures ANOVAs were also conducted across 5 min time bins separately for days 1 and 10. For each day, time bin was the repeated measure and treatment (saline, 3 and 10 mg/kg cocaine) was the between-subjects variable. Independent ANOVAs and Fisher's LSD multiple comparisons served as posthoc analyses where appropriate.

Other behaviors including preening, pecking, and feather fluffing were analyzed similarly as distance traveled on days 1 and 10. Duration of preening was measured when birds cleaned or straightened their feathers with their beaks. The frequency of pecks made to the floor and walls was measured. Preening and pecking were chosen based on previous research [22]. The frequency of feather fluffing, which was signified by a bird puffing out their feathers was also measured because several instances of it were observed early in the experiment. All data were analyzed using SPSS software version 22 (International Business Machines Corp. (IBM), Armonk, NY). A Grubb's test was utilized in each treatment group before analyses to remove outliers. One outlier from the 10 mg/kg group was removed from the final dataset using this method. The final sample size for the current experiment was 23. The level of statistical significance was chosen as $p < 0.05$.

3. RESULTS

Fig. (**1**) represents the mean distance traveled for subjects that received saline, 3 or 10 mg/kg IM injections on Day 1 and 10. A repeated-measures ANOVA revealed a significant Treatment x Day interaction, F (2, 20) = 4.2. Independent repeated-measures ANOVAs showed that subjects that received 3 mg/kg cocaine had significantly greater distance traveled on Day 10 (M=13.91, SEM 2.44) compared to Day 1 (M=6.20, SEM=1.27), F (1, 7) = 8.42. Neither saline nor the 10 mg/kg cocaine treatment resulted in increased distance traveled from Day 1 to Day 10, F's ranged from 0.03-0.7.

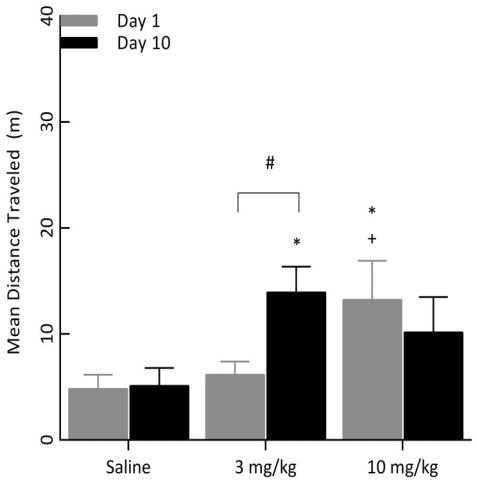

Fig. (1). Mean distance traveled (m) + SEM on Day 1 and Day 10 for saline, 3 and 10 mg/kg cocaine. * indicates significant difference for saline, + indicates significant difference from 3 mg/kg cocaine, and # indicates significant difference of Day 1 vs. Day 10, $p < 0.05$.

A separate one-way ANOVA on Day 1 indicated that subjects treated with 10 mg/kg cocaine had greater distance traveled compared to subjects treated with 3 mg/kg cocaine and saline, F (2, 22) = 3.9. On Day 10, no treatment groups differed in distance traveled, F = 3.3.

Fig. **2** represents the mean distance traveled in 5 min Time bins for subjects treated with saline, 3, or 10 mg/kg cocaine on Day 1 (Fig. **2A**) and Day 10 (Fig. **2B**). A repeated-measures ANOVA indicated that on Day 1 there was a significant Time bin x Treatment interaction, F (10, 100), 2.49, $p < 0.05$. Independent one-way ANOVAs revealed treatment differences in distance traveled for Time bins 4, 5, and 6, F's ranged from 5.2 to 5.7. Significant main effects of Treatment (F (2, 20) =3.9) and Time bin (F = 2, 20) = 9.4 were also evident on Day 1.

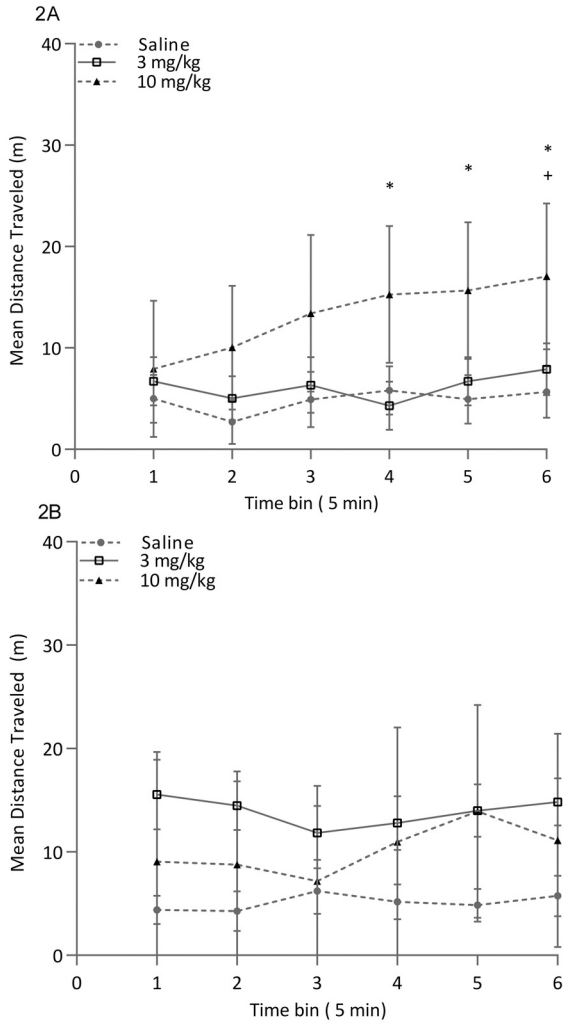

Fig. (2). Mean distance traveled across 6, 5 min time bins for saline, 3 and 10 mg/kg cocaine of Day 1 (2A) and day 10 (2B). Error bars are ± SEM. * indicates 10 mg/kg cocaine group significantly different from saline and 3 mg/kg cocaine, + indicates 10 mg/kg cocaine group significantly different from time bin 1 to time bin 6.

Further analysis showed that subjects that received 10 mg/kg cocaine had significantly greater distance traveled on Time bin 6 (M=17.06, SEM=4.35) compared to Time bin 1 (M=7.94, SEM=3.51), F (1,6) = 10.24. For Day 10 (Fig. **2B**), a repeated measures ANOVA failed to reveal a significant Treatment x Time bin interaction, F (10, 100) = 1.44.

Administration of IM cocaine on other behaviors was investigated with a repeated-measures ANOVA with Day as a repeated measure (1 and 10) and Treatment as a between-subjects factor. There were no significant Treatment x Day interactions for frequency of pecking or duration of preening, where F's were 0.51 to 0.45, respectively. There were also no significant main effects of treatment for pecking or preening, as F's were 2.8 and 0.21, respectively.

A repeated measures ANOVA for the frequency of feather fluffing revealed a near significant Treatment x Day interaction, F (2, 19) = 6.78, p = 0.52, and a main effect of Treatment, F (2, 19) = 8.32. Fisher's LSD post hoc analysis indicated that birds that received saline (M=2.69, SEM=0.25) had a higher frequency of feather fluffs compared to birds that received 3 mg/kg cocaine (M=1.29, SEM=0.25) and 10 mg/kg cocaine (M=1.64, SEM=0.26).

4. DISCUSSION

Results showed that cocaine-induced behavioral sensitization occurred when birds were given IM administration of 3 mg/kg cocaine. These subjects had a cocaine-induced increase in locomotor activity from day 1 to day 10. While sensitization was not evident for birds given IM administration of 10 mg/kg, those birds showed the greatest locomotor activity on day 1 and this activity appeared to decrease by day 10. Cocaine did not appear to have any significant effects on duration of preening or frequency of pecking. However, the frequency of feather fluffing decreased from day 1 to day 10 for both cocaine doses relative to saline.

The current findings are consistent with previous research investigating the effects of IM cocaine administration in pigeons and they further validate the use of the apparatus developed by Pinkston and Branch [22] to measure drug-induced locomotor activity effects in birds. Pinkston and Branch [22] observed a cocaine-induced increase

in locomotor activity in pigeons that received IM administration of 1, 3, and 10 mg/kg cocaine. Previous studies on IP administration of cocaine have been conducted in Japanese quail. These studies reported behavioral sensitization and increased locomotor activity when quail were given IP injections of 10 and 23 mg/kg cocaine but not 5 mg/kg [10, 12]. The current findings on IM administration and Pinkston and Branch's work with pigeons [22] suggest that IM injections of cocaine may be relatively more potent than IP injections and thereby induce cocaine sensitization and tolerance at lower doses and more acutely.

The current findings for IM administration of 10 mg/kg cocaine were unique to the previous literature with pigeons [22]. Rather than demonstrating cocaine-induced behavioral sensitization, this treatment induced a high level of locomotor activity acutely that appeared to decrease with chronic administration. This is perhaps an indication of behavioral tolerance. In rodents, behavioral tolerance is induced with relatively high doses of IP cocaine (*e.g.*, 40 mg/kg) or continuous long-term exposure to IP cocaine [32]. The current findings indicate that tolerance may have been evident with a relatively low dose of IM cocaine and shorter exposure. This provides additional evidence for increased potency of cocaine with the IM route of administration.

Differences in potency of IM and IP cocaine administration may be due to differences in metabolism. IP administration undergoes the first-pass metabolism, which reduces the bioavailability of the drug [21]. However, IM injections avoid much of the first-pass metabolism, with 50-70% lower doses than IP while providing a similar plasma concentration [19, 21]. Thus, the bioavailability of cocaine depends on the route of administration [21, 33].

Typically, in both rodents and quail, cocaine sensitization is measured during 30 min locomotor activity sessions with IP injections of cocaine [11, 14, 15]. Pinkston & Branch [22] gave 150 min cocaine locomotor activity sessions. This difference in session length and other methodological differences might explain some of the differences between the present study and their study. However, previous cocaine IP studies conducted in our laboratory utilized the same session length and dose of cocaine as in the current experiment [11, 12]. The only difference was the route of administration (IP versus IM). Those studies reported cocaine sensitization with IP injections rather than what appears to be tolerance with IM injections in the current experiment. Therefore, session length did not appear to play a role in the acquisition of tolerance in the current experiment.

Similar to the findings of Pinkston and Branch [22], surprisingly IM cocaine did not appear to affect pecking behavior. This is in contrast to the previous finding that the direct dopamine agonist apomorphine elicits drug-induced pecking in pigeons [34]. Furthermore, Pinkston and Branch [22] observed a dose-dependent decrease in preening behavior in pigeons that received IM cocaine. The current study did not find an effect of IM cocaine on preening behavior but it did find that IM cocaine decreased feather fluffing compared to IM saline. Typically, feather fluffing occurs during hypothermia and occurs with shivering [35]. Cocaine has been shown to increase core body temperatures of rodents [33]. Therefore, although speculative, it may be that in the current study, IM administration of cocaine increased the core body temperature of the birds and this resulted in a decrease in the occurrence of feather fluffing.

CONCLUSION

In summary, the present study suggests that IM cocaine administration may be a relatively potent route of administration that should be considered for future substance abuse research in some species. Because the route of administration of cocaine plays a role in the pharmacokinetics of cocaine and its addictive properties, the IM route of administration may be of additional benefit for studying drug addiction research. It should be noted that the methods for assessing behavioral sensitization in rodents and quail are comparable for the most part.

ETHICAL STATEMENT

This work reported experiments in accordance with the standards set forth in the 8th Edition of Guide for the Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/Guide-for-thecare-and-use-oflaboratory-animals.pdf) published by the National Academy of Sciences, The National Academies Press, Washington DC, United States of America.

CONFLICT OF INTEREST

The authors (Rice, Tariq, & Akins) declare no conflict of interest and all of the authors contributed substantially to this article.

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