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Neither non-contingent electric footshock nor administered corticosterone facilitate the acquisition of methamphetamine self-administration

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Abstract

Previous research has indicated a role for the hypothalamo–pituitary–adrenal (HPA) axis in the acquisition of intravenous cocaine self-administration since both exposure to stressors and exogenous injections of corticosterone facilitate this behavior. The present experiment was designed to determine whether electric footshock or pretreatment with corticosterone would produce similar effects on the acquisition of methamphetamine self-administration in male Wistar rats. Following initial food training, the rats were allowed to self-administer methamphetamine in ascending doses (0.0075–0.12 mg/kg/infusion) that were doubled weekly. Neither non-contingent electric footshock nor treatment with corticosterone (2.0 mg/kg, i.p.) affected the lowest dose at which the rats first acquired methamphetamine self-administration (0.015 mg/kg/infusion). The treatment groups all had similar inverted "U"-shaped acquisition curves typical of psychostimulants. Although these experiments do not indicate a major role for the HPA axis in the acquisition of methamphetamine self-administration, more studies need to be conducted to further evaluate the effects of the HPA axis on the acquisition of methamphetamine self-administration before a potential role can be ruled out.

Keywords: HPA axis; Corticosterone; Electric footshock; Methamphetamine; Acquisition; Self-administration; Reward

1. Introduction

Studies using animal models of self-administration have found that the acquisition of psychostimulant self-administration is increased in rats exposed to stress. Repeated tail pinch (Piazza et al., 1990), social stress (Tidey and Miczek, 1997; Miczek and Mutschler, 1996; Haney et al., 1995), and social isolation (Howes et al., 2000; Kosten et al., 2000; Schenk et al., 1987) have all been found to accelerate the acquisition of psychostimulant self-administration. However, while pre-clinical research has investigated the effects of stress on the acquisition of cocaine and amphetamine self-administration, there have been no published reports on the effects of stress on methamphetamine self-administration.

Previous research conducted by our laboratory has shown that non-contingent electric footshock facilitates the acquisition of cocaine self-administration (Goeders and Guerin, 1994). The acquisition dose–response curve for rats receiving non-contingent footshock was shifted upward and to the left compared to rats receiving contingent footshock or non-shocked controls, indicating that these rats were more sensitive to low doses of cocaine. Plasma corticosterone was positively correlated with cocaine self-administration in all three groups at the 0.125 mg/kg/infusion dose of cocaine, the dose at which some rats acquired self-administration. Rats exposed to non-contingent footshock exhibited the highest plasma corticosterone and readily acquired self-administration at the 0.125 mg/kg/infusion dose. Later experiments were designed to explore the effects of adrenocorticosteroids on the acquis-

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ition of cocaine self-administration (Mantsch et al., 1998). In these experiments rats receiving daily injections of vehicle or corticosterone (2 mg/kg, i.p.) were presented with ascending concentrations of cocaine (0.031–0.5 mg/kg/infusion). Corticosterone pretreatment facilitated the acquisition of cocaine self-administration, indicating that elevated plasma corticosterone influences the acquisition of cocaine self-administration.

The present experiments were therefore designed to assess the effects of stress and the subsequent activation of the HPA axis on the acquisition of methamphetamine self-administration. Stress, in the form of non-contingent electric footshock was used to activate the HPA axis and thereby elevates plasma corticosterone. The effects of parentally administered corticosterone on the acquisition of methamphetamine self-administration were also evaluated.

2. Materials and methods

2.1. Subjects

Sixty, male Wistar rats, (Harlan Sprague–Dawley) 80 to 100 days old at the start of the experiment were used. All rats were housed in individual cages equipped with a laminar flow unit and air filter in a temperature- and humidity-controlled AAALAC-accredited animal care facility on a reversed 12-h light–dark cycle (lights on at 7:00 PM). Rats were maintained at 85% to 90% of their free-feeding body weights by presentations of food pellets (P.J. Noyes; 45 mg) during behavioral sessions when applicable and/or by supplemental feeding (Purina Rat Chow) and had access to water ad libitum. All procedures were approved by the LSUHSC-S animal care and use committee and were carried out in accordance with the NIH "Principles of Laboratory Animal Care" (NIH publication No. 85-23).

2.2. Venous catheterization and drug delivery

Each rat was implanted with a chronic indwelling jugular catheter under sodium pentobarbital anesthesia (50 mg/kg, i.p.) with methylatropine nitrate pretreatment (10 mg/kg, i.p.) using previously reported procedures (Koob and Goeders, 1989; Goeders et al., 1998). The animals were also injected with sterile penicillin G procaine suspension (75,000 U, i.m.) immediately before surgery, and they were allowed a minimum of 4 days to recover following surgery. The catheter (0.3048 mm i.d.×0.635 mm o.d., silicone tubing) was inserted into the right posterior facial vein and pushed down into the jugular vein until it terminated outside the right atrium. The catheter was anchored to tissue in the area and continued subcutaneously to the back where it exited at the base of the skull. The catheter was connected to a 22-gauge guide cannula (Plastic Products) which was mounted to the top of the skull using dental acrylic and stainless-steel screws for attachment of a leash. The stainless-steel spring leash (Plastic Products) was attached to the guide cannula assembly and to a leak-proof fluid swivel suspended above the operant chamber. Tubing connected the swivel to a 20-ml syringe in a motor-driven pump (Razel) located outside the sound attenuating enclosure. The swivel and leash assembly was counter-balanced to permit relatively unrestrained movement of the animal and was connected during all experimental sessions. At the end of each session, the leash was disconnected, the catheter was filled with streptokinase (816,000 IU) to inhibit the formation of blood clots and a dummy cannula was inserted into the guide before the rat was returned to its home cage. The patency of the catheters was tested immediately after the end of the session each Wednesday. If blood could be obtained via the catheter, then it was judged to be patent. If not, then the rat was injected via the catheter with methohexital sodium (1.5 mg, i.v.). An immediate light anesthesia indicated that the catheter was functional.

2.3. Apparatus

Standard plastic and stainless-steel operant conditioning chambers contained within sound-attenuating enclosures (Med-Associates) were used to run the behavioral experiments. Each experimental chamber was equipped with two retractable response levers (Med-Associates) mounted on either side of the chamber, with a stimulus light located above each lever. The enclosures contained an exhaust fan that supplied ventilation and white noise to mast extraneous sounds. An IBM-compatible computer and interface system (Med-Associates) was used to program the procedures and collect the experimental data.

2.4. Food and self-administration training

The rats were initially trained to respond for food pellets (45 mg) during daily 1-h test sessions for the first week. During these sessions, the food response lever was extended into the chamber and the corresponding lever light illuminated to indicate availability of food reinforcement. Each response on the food lever resulted in a brief darkening of the food stimulus light (0.6 s) and the delivery of a single food pellet. Sessions were terminated after 60 min or when 100 food pellets were delivered. The first day of the week (Monday) remained a food training session throughout the experiment to maintain lever-pressing behavior and as a control for the potential nonspecific effects of the various treatments.

During daily 1-h methamphetamine acquisition sessions, the drug response lever was extended into the chamber with the corresponding stimulus light above the lever illuminated. Responding on the drug lever (fixed-ratio 1) resulted in an infusion of saline or methamphetamine (200 μl over

5.6 s) followed by a 20-s timeout period during which the lever was retracted and the lever light extinguished. Saline was available for self-administration during the first 2 weeks following food training to establish an operant baseline. During the following weeks, methamphetamine was available 4 days each week at a dose starting at 0.0075 mg/kg/infusion, and the dose was doubled each subsequent week until the final concentration of 0.12 mg/kg/infusion was reached. Ascending doses of methamphetamine were used to prevent sensitization. The data during the final 3 days of the week (Wednesday through Friday) were used to determine the acquisition dose–response curve since a high rate of responding typically occurred during the first self-administration session following the food training session each Monday.

2.5. Treatment groups

The rats in the non-contingent footshock group (n=20) received approximately 50 electric footshocks (0.6 mA, 0.1s in duration) on a variable-interval 74-s schedule (mean interval: 74 s, range: 30–144 s) during 1-h sessions that were conducted immediately prior to each food training and self-administration test session. Electric footshock began on the first day of food training and continued 5 days a week throughout the duration of the experiment. Control rats (n=10) were placed in the experimental chamber 1-h prior to the start of the self-administration session, but no footshock was delivered. The chamber remained darkened during both conditions. Rats in the remaining groups received either corticosterone (n=20; 2.0 mg/kg, i.p.) or vehicle (n=10; 5% emulphor in bacteriostatic 0.9% saline, i.p.) in their home cages 15 min prior to the start of the food training or self-administration session. Data from the rats in the no shock control and vehicle groups were combined into a single control group due to the lack of statistically significant differences between the groups and for the sake of simplicity in presenting the data. The vehicle and corticosterone treatments were administered 7 days a week, starting with the first day of food training, and continued for the duration of the experiment. The data obtained from three rats (1 control, 2 corticosterone treated) were excluded due to loss of catheter patency during the experiment.

2.6. Plasma corticosterone measurements

Blood (250–300 μl) was obtained via the implanted catheters for the determination of plasma corticosterone. If post-session blood could not be readily obtained from the catheter, the rat was lightly anesthetized with methohexital sodium (5 mg, i.v.) and tail blood was obtained. Blood was collected prior to the start of the weekly food training sessions to test for potential long-lasting effects of electric footshock and corticosterone treatments on plasma corticosterone. Blood was also collected immediately following self-administration on the last session of the week to determine the effects of methamphetamine on plasma corticosterone. Plasma corticosterone (ng/ml) was determined by specific radioimmunoassay using the ImmuChem antibody [^{125}I] corticosterone kit (ICN Biomedical).

2.7. Drugs

Methamphetamine was obtained from the National Institute on Drug Abuse (Research Triangle Park, NC) and was dissolved in bacteriostatic, heparinized 0.9% saline. Corticosterone (Sigma) was suspended in 5% emulphor and administered in a volume of 1 ml/kg, i.p.

2.8. Statistical analysis

Data collected during the self-administration sessions included the mean number of methamphetamine infusions per session for each dose of methamphetamine and the mean rate of food-reinforced responding during the weekly food sessions. Self-administration sessions were conducted Tuesday through Friday and the means were determined from data collected during the final 3 sessions for each dose (i.e., Wednesday through Friday). Acquisition was defined as the first dose where the mean number of infusions differed significantly from baseline infusions during saline self-administration. A repeated measures analysis of variance was used to determine the effects of treatment with a within subjects factor of dose, on the number of infusions received per session (STATISTICA, v.6.0; StatSoft, Tulsa, OK). Post-hoc analyses for self-administration were preformed using the Tukey HSD test. The effects of treatment and dose on pre- and post-session plasma corticosterone concentrations were also analyzed using repeated measures ANOVA. Post-hoc analyses of the differences in plasma corticosterone were performed using Fishers LSD test.

3. Results

3.1. Effects on food-reinforced responding

Table 1 shows the mean rates of food-reinforced responding for the three treatment conditions (i.e., control, footshock, and corticosterone) on the Friday of the initial food training week and on Mondays prior to testing each dose of methamphetamine for self-administration. There were no significant differences in the rates of food-reinforced responding among the groups at any of the doses tested [treatment, $F(6,111)=2.790$, $p<0.05$]. However there was a significant effect of dose [$F(6,306)=8.448$, $p<0.001$]. Rats in the corticosterone treatment group had higher rates of responding at the 0.03 ($p<0.05$), 0.06 ($p<0.05$), and the 0.12 ($p<0.001$) mg/kg doses compared to baseline rates of responding measured prior to saline self-administration.

Table 1
Rates of food-reinforced responding (mean responses/min±S.E.M.) for treatment groups during food sessions corresponding to the weeks during which the various doses of methamphetamine were available for self-administration

Treatment	Baseline	Saline	Response rate				
			0.0075	0.015	0.03	0.06	0.12
Control	9.64±1.32	10.99±1.06	11.92±1.24	12.73±0.91	12.92±1.03	12.88±0.85	12.29±1.36
Cort	10.51±1.38	11.33±1.04	11.99±1.17	14.34±1.44	14.89±1.56*	14.85±1.24*	16.58±1.38**
Shock	12.24±0.73	12.99±0.81	13.43±0.95	13.37±1.05	14.60±1.05	15.11±0.94	14.69±1.11

* $p<0.05$ vs. baseline.
** $p<0.001$ vs. baseline.

3.2. Effects on the acquisition of methamphetamine self-administration

Fig. 1 illustrates the effects of non-contingent electric footshock and pretreatment with corticosterone on the acquisition of methamphetamine self-administration. The acquisition of methamphetamine self-administration was not facilitated by either non-contingent footshock or exogenously administered corticosterone [treatment, $F(2, 165)=2.158$, $p=0.1188$]. However, there was a significant effect of dose [$F(5, 825)=66.812$, $p<0.001$] with all three groups acquiring methamphetamine self-administration at the 0.015 mg/kg/infusion dose ($p<0.001$ for all three treatment conditions).

3.3. Effects on plasma corticosterone

Pre-session plasma corticosterone did not differ significantly across treatment groups (control: 273±16 ng/ml, corticosterone: 333±16 ng/ml, shock: 274±15 ng/ml). Furthermore, pre-session blood, which was taken prior to the start of the Monday food session each week, did not significantly differ from baseline for any of the treatment groups at any time point during the course of the experiment (data not shown).

However, self-administered methamphetamine produced significant dose-related increases in plasma corticosterone [$F(5, 10)=7.1643$, $p<0.001$] in each of the three treatment groups (Fig. 2). Post-session plasma corticosterone was significantly elevated in control and shock rats at the 0.03 and 0.06 mg/kg/infusion doses compared to post-session corticosterone following saline self-administration ($p<0.05$ for each). In rats receiving exogenous injections of corticosterone, post-session corticosterone was slightly elevated at the 0.03 mg/kg/infusion dose ($p=0.07$) and significantly elevated at the 0.06 mg/kg/infusion dose ($p<0.05$) compared to post-session corticosterone following saline self-administration.

4. Discussion

In this series of experiments an attempt was made to: (1) activate the HPA axis by exposing rats to a stressor (i.e., non-contingent electric footshock) and (2) mimic HPA axis activation by administering exogenous cortico-

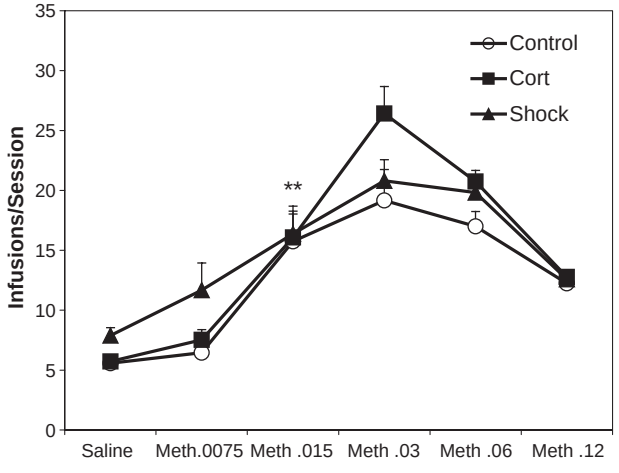

Fig. 1. Acquisition dose–response curves for intravenous methamphetamine self-administration in rats pretreated daily with corticosterone (2.0 mg/kg i.p.; $n=18$; Cort), vehicle (5% emulphor in bacteriostatic 0.9% saline, i.p.; $n=19$; Control), or exposed to non-contingent electric footshock ($n=20$; Shock). Data points represent the mean number of infusions per session±S.E.M. **$p<0.001$ vs. saline.

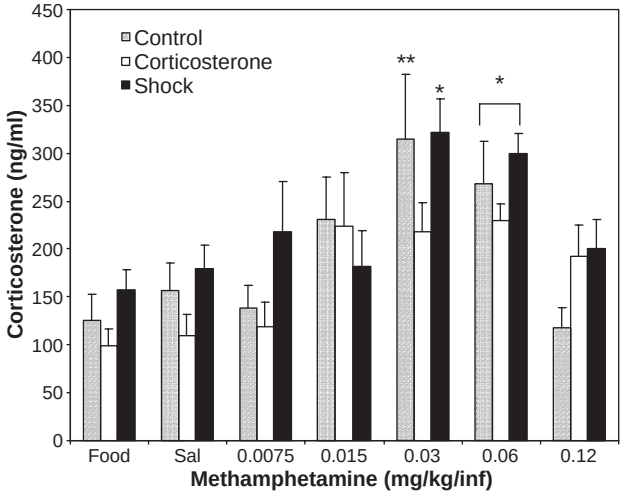

Fig. 2. Plasma corticosterone (ng/ml) measured in blood collected immediately following the behavioral sessions in rats pretreated with vehicle ($n=16$), corticosterone ($n=14$), or exposed to non-contingent electric footshock ($n=16$). Data are presented as the means±S.E.M. *$p<0.05$ vs saline.

sterone. Neither of the treatments facilitated the acquisition of methamphetamine self-administration. The two treatment groups and the control group all acquired self-administration at the 0.015 mg/kg/infusion dose and displayed an inverted "U"-shaped acquisition curve typically seen with psychostimulants.

Neither pre- nor post-session plasma corticosterone was affected by either exogenously administered corticosterone or non-contingent electric footshock. However, post-session plasma corticosterone was significantly increased in the control and shock groups at the doses of methamphetamine where the highest rates of self-administration were seen (i.e., 0.03 and 0.06 mg/kg/infusion) when compared to plasma corticosterone measured following saline self-administration. Rats receiving exogenous injections of corticosterone also had slightly elevated post-session plasma corticosterone at the 0.03 mg/kg/infusion dose and significantly elevated plasma corticosterone at the 0.06 mg/kg/infusion dose of methamphetamine. Other laboratories have reposted that a single injection of methamphetamine transiently increases plasma corticosterone compared to saline-treated controls (Asano and Moroji, 1974; Szumlinski et al., 2001). There is also evidence of a methamphetamine-induces rise in plasma cortisol in humans (Fehm et al., 1984), although this effect has not been seen in all studies (Gouzoulis-Mayfrank et al., 1999). The short plasma half-life of corticosterone (Sainio et al., 1988) may explain why plasma corticosterone was not elevated in the corticosterone-treated group since post-session blood was collected 1 h and 15 min after the injection of corticosterone. Nevertheless, this experimental design was very similar to the one in which we showed that corticosterone facilitates the acquisition of cocaine self-administration (Mantsch et al., 1998), although post-session plasma corticosterone was not measured in that study. Pre-session plasma corticosterone was rather high in the present study ($\approx$275 ng/ml), which could simply be attributed to stress from handling the rats before the session (Dobrakovova and Jurcovicova, 1984). This elevated pre-session plasma corticosterone has also been observed in rats trained to self-administer cocaine, and may be explained by an anticipatory or conditioned effect of the drug reinforcer (Goeders and Clampitt, 2002).

We have previously demonstrated that non-contingent electric footshock facilitates the acquisition of cocaine self-administration (Goeders and Guerin, 1994). Similar results were not seen for the acquisition of methamphetamine self-administration in the present study. One possible explanation for this discrepancy is the difference in methodology. The cocaine acquisition experiment contained a multiple schedule of reinforcement, with food pellets available during the first component and cocaine during the second. Footshock was delivered during this first component of the multiple schedules although footshock delivery was not contingent on food lever responding in the group exhibiting the largest effects on cocaine self-administration (i.e., the non-contingent shock group). The frequency of footshocks delivered in the present study was intentionally set to match the frequency and distribution of footshocks delivered in the former study. Nevertheless, the ability of the rats to respond for food reinforcement while receiving footshocks was lacking in the current experiments and may explain the lack of effect of non-contingent footshock on the acquisition of methamphetamine self-administration compared to non-shocked controls.

Interestingly, plasma corticosterone was not significantly elevated in the footshock group compared to the other groups in the current experiment, which is unlike what we observed in the cocaine acquisition experiment. In the cocaine experiment, blood was collected for the determination of plasma corticosterone concentrations immediately following the shock session prior to the start of cocaine self-administration. The rats in the non-contingent shock group had elevated plasma corticosterone (162.0 ± 21.2 ng/ml) compared to no shock controls (68.4 ± 6.6 ng/ml). These plasma corticosterone levels were much lower than what was seen in the current experiment when blood was collected prior to any treatment or behavioral session.

The failure of electric footshock to elevate plasma corticosterone may be due to habituation to footshock. Other groups have shown a habituation of corticosterone responses in rats repeatedly exposed to low intensity electric footshock (Pitman et al., 1990; Kant et al., 1987). Food-reinforced responding concurrent with footshock delivery may have mitigated the development of habituation in our former study.

Finally, the differences observed in the effects of non-contingent footshock and corticosterone pretreatment on the acquisition of methamphetamine compared to cocaine self-administration may be due to the differences in the drugs themselves. Although the reinforcing and behavioral effects of both cocaine and methamphetamine are hypothesized to be due in large part to the ability of these agents to potentiate dopamine neurotransmission in mesocorticolimbic neural pathways (DiChiara and Imperato, 1988; Kuhar et al., 1991; Wise and Bozarth, 1987), they also differ in important ways. Methamphetamine, like amphetamine and unlike cocaine, has the ability to enhance neurotransmitter release by causing a reversal of transporter function (Jones et al., 1999; Fleckenstein et al., 2000). The administration of methamphetamine in vivo has also been shown to cause a rapid and reversible decrease in serotonin and dopamine receptor function in striatal synaptosomes, while high doses of cocaine have no effect (Fleckenstein et al., 1999). Methamphetamine also has profound neurotoxic effects on serotonergic and dopaminergic neurons (Axt and Molliver, 1991; Cappon et al., 2000). Woolverton et al. (1989) reported decreases in dopamine and serotonin in the caudate nucleus of rhesus monkeys 4 years after chronic methamphetamine administration was terminated. Chronic cocaine use is not

usually associated with such long-lasting neurotoxic effects. The aforementioned neurophysiological differences between cocaine and methamphetamine may explain the behavioral differences we observed in the acquisition of self-administration of these drugs.

However, stress and the subsequent activation of the HPA axis have also been shown to impact the acquisition of amphetamine self-administration (Piazza et al., 1990, 1991). While methamphetamine and amphetamine share the same basic neurobiological profile, there are significant differences. For example, although methamphetamine and amphetamine have an equivalent potency for blocking norepinephrine uptake, methamphetamine is a less potent inhibitor of dopamine uptake. Regional differences between the methamphetamine- and amphetamine-induced release of dopamine and glutamate have also been observed (Shoblock et al., 2003a). Both drugs deplete dopamine in response to repeated administration in the caudate nucleus. However, only methamphetamine depletes serotonin in the caudate nucleus and nucleus accumbens (Segal and Kuczenski, 1997). Behavioral differences between methamphetamine and amphetamine have also been observed, such as their effects on locomotion (Shoblock et al., 2003a) and working memory (Shoblock et al., 2003b).

In summary, this study found that neither exposure to non-contingent electric footshock nor exogenous injections of corticosterone facilitated the acquisition of methamphetamine self-administration. Neither method of experimentally-induced rise in plasma corticosterone concentration affected the dose at which methamphetamine self-administration was acquired or shifted the acquisition curve relative to control rats. It remains unclear if the methods employed in the current study to increase plasma corticosterone truly caused a rise in plasma corticosterone concentrations. Previous studies using similar methods found that exogenously administered corticosterone or exposure to non-contingent footshock facilitated the acquisition of cocaine self-administration (Mantsch et al., 1998; Goeders and Guerin, 1994). This study suggests that the HPA axis does not play a strong a role in the acquisition of methamphetamine self-administration as seen with cocaine self-administration. Further studies are needed before a potential role for the HPA axis can be ruled out.

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