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European Journal of Pharmacology 455 (2002) 117–126

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Cocaine-induced hypophagia and hyperlocomotion in rats are attenuated by prazosin

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Received 3 June 2002; received in revised form 8 October 2002; accepted 15 October 2002

Abstract

The present studies examined the effects of antagonizing α_1-adrenoceptors via systemic administration of prazosin on the behavioral actions of cocaine in rats, including induction of locomotion and suppression of eating. In Experiment 1, locomotor activity was monitored in automated chambers for 80 min in adult male rats pretreated with the α_1-adrenoceptor antagonist prazosin (0, 0.5, or 2 mg/kg, i.p.) and then treated (i.p.) with either 0, 10, 20, or 40 mg/kg cocaine hydrochloride. Cocaine dose-dependently increased total distance traveled and the number of stereotypy counts, and significantly decreased rest time. Each dose of prazosin produced a significant attenuation of the locomotor effects of a limited range of cocaine doses (i.e. 10 and/or 20 mg/kg cocaine, but not 40 mg/kg cocaine). Prazosin alone did not alter any measure of locomotion. In Experiment 2, eating and drinking were monitored for 60 min in male rats pretreated with prazosin (0, 1, and 2 mg/kg, i.p.) and then treated with 0, 10, 20, or 40 mg/kg (i.p.) cocaine. Rats pretreated with vehicle exhibited a dose-dependent suppression of eating, but not drinking, to cocaine. The impact of prazosin on cocaine-induced hypophagia paralleled that noted for locomotion in that administration of prazosin significantly attenuated the hypophagic action of 20 mg/kg cocaine, but not that of 40 mg/kg cocaine. These findings confirm earlier studies noting a partial role for α_1-adrenoceptors in the locomotor stimulant actions of cocaine and extend those findings to the feeding-inhibitory actions of cocaine.

Keywords: Dopamine; Norepinephrine; α_1-Adrenoceptor; Cocaine; Prazosin; Hypophagia; Hyperlocomotion; (Rat)

1. Introduction

Inactivation by cocaine of neuronal membrane transporter proteins increases extracellular levels of dopamine, norepinephrine, and serotonin (Rothman et al., 2001), which may act in multiple brain regions via multiple pathways to influence behavioral activation (Woolverton and Kleven, 1988). Pharmacological antagonism of dopamine receptors, for example, attenuates the locomotor activating effects of cocaine (Baker et al., 1996; Bhattacharyya et al., 1979), whereas inactivation of the α_1-adrenoceptor subtype, using the antagonist prazosin, has yielded mixed results. Thiebot et al. (1981) reported no significant alteration of cocaine-induced locomotion by prazosin, while other studies report that prazosin significantly attenuates the stimulatory actions of cocaine on locomotor activation (Drouin et al., 2002a; Snoddy and Tessel, 1985; Tessel and Barrett, 1986). These studies vary widely in procedural details, which may contribute to the different outcomes. The former study employed single doses of cocaine (4 mg/kg) and prazosin (0.25 mg/kg) in mice, while the latter studies commonly used a single dose of cocaine and/or prazosin in rats (Drouin et al., 2002a) and a global measure of locomotion (e.g. Berthold et al., 1992; Drouin et al., 2002a). Confirmation of an attenuation of cocaine activity by prazosin would suggest that norepinephrine, acting via noradrenergic receptors, may contribute to the behavioral actions of cocaine.

Drugs that increase extracellular norepinephrine via blockade of reuptake can inhibit eating (Jackson et al., 1997a,b; Gehlert et al., 1998), whereas overeating accompanies the loss of brain norepinephrine innervation produced by ablation of the ascending ventral noradrenergic bundles (Ahlskog, 1974). Sympathomimetic drugs such as phenylpropanolamine, ephedrine, or cirazoline are known to directly or indirectly activate α_1-adrenoceptors and these

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PII: S0014-2999(02)02616-X

drugs are known to inhibit eating in the rat (Fox et al., 1985; Minneman et al., 1983; Wellman et al., 1993). Moreover, prazosin administration attenuates the hypophagia in rats induced by a series of sympathomimetic drugs including amphetamine, ephedrine, phenylpropanolamine, aminorex, and phentermine (Jackson et al., 1997a; Mitchell et al., 1998; Wellman et al., 1993, 2003, in press). The capacity of cocaine to inhibit eating in the rat is attenuated by pharmacological antagonism of dopamine receptors (Cooper and van der Hoek, 1993; Heffner et al., 1977; Rapoza and Woolverton, 1991), but the hypophagic action of cocaine is not completely mimicked by dopamine receptor subtype agonists (Cooper et al., 1990; Rusk and Cooper, 1989). These results suggest that cocaine may act in part on non-dopaminergic substrates to inhibit eating in the rat.

The intent of the present experiments was therefore to further examine the impact of antagonism of α_1-adrenoceptors using prazosin on the behavioral effects of cocaine in rats. Experiment 1 considered the impact of 0.5 and 2.0 mg/kg prazosin on multiple measures of locomotion (e.g. total distance traveled, stereotypy counts, rest time) in rats treated with a full range of cocaine doses (0, 10, 20, or 40 mg/kg). Experiment 2 considered whether prazosin (0, 1, and 2 mg/kg) produced a similar attenuation of the hypophagic action of cocaine (0, 10, 20, or 40 mg/kg) in rats.

2. Materials and methods

2.1. Experiment 1

2.1.1. Animals

Eighty-four Sprague–Dawley albino rats (Harlan Industries, Houston, TX) weighing 265–310 g at the start of the experiment were housed individually in hanging wire rodent cages in a colony room maintained at 21.0 ± 1 °C under a 12:12 h illumination schedule (lights on at 0800 h).

2.1.2. Drugs

A vehicle solution was prepared using sterile distilled water and 0.9% (w/v) sodium chloride. Solutions of cocaine hydrochloride (10, 20, or 40 mg/ml) and prazosin hydrochloride (0.5 or 2 mg/ml) were prepared in sterile vehicle prior to injection. All drugs were obtained from Sigma (St. Louis, MO). Drug doses were calculated as the salt and all injections were administered i.p. at a volume of 1 ml/kg.

2.1.3. Apparatus

Multiple measures of locomotion were monitored in this study using an automated Versamax system (Accuscan Instruments, Columbus, OH). Each of six optical beam activity monitors (Model RXYZCM-16) was comprised of 16 vertical and 16 horizontal infrared sensors. Each activity monitor was enclosed within an acrylic cage (40 × 40 × 30.5 cm). The ceiling of each cage consisted of a hinged Plexiglas lid (43 × 43 cm), through which a series of 0.5-cm holes were drilled to provide ventilation. The activity monitors and associated hardware were located in a testing room. Each of the six chambers was connected to a multiplexor-analyzer (Versamax: Model VMA16) interfaced with an IBM-compatible microcomputer. During locomotor testing, an overhead 40-W red light bulb provided illumination within the testing room and extraneous noise within the room was masked using a white noise generator.

2.1.4. Procedure

The rats were run in squads on 3 consecutive days, starting each day at about 0830 h. The rats were transferred from the home cage into separate plastic containers and transported to the locomotor testing room. On day 1, the rats were placed into their respective activity cages for 10 min, removed and handled briefly, and then returned to the activity chamber for another 10-min period. The rats were again removed, handled, and then placed into the activity chambers for a final 60-min test period. On day 2, the procedures were as on day 1, except that the rats were injected with vehicle (1 ml/kg, i.p.) at − 10 min and then again with vehicle immediately prior to the 60-min test session. On day 3, the procedures were as on day 2, except that the rats were injected (i.p.) with either 0, 0.5, or 2 mg/kg prazosin at − 10 min, and were then injected (i.p.) with 0, 10, 20, or 40 mg/kg cocaine immediately prior to the 60-min test session. The overall sequence of pretreatment and treatment injections on day 3 is summarized in Fig. 1.

Locomotor activity was monitored across successive 5-min periods during each phase of the test sessions. At the end of each session, the rats were returned to the home cage in the colony room. The test chambers were then cleaned thoroughly with a mild Lysol (1 teaspoon per 10 oz) solution and thoroughly dried prior to the next test session. Because of the limits imposed by the number of chambers available for testing, this study was run in three separate replications. In each replication, four to six squads were run each day with each squad composed of two to six rats. Each replication contained similar numbers of rats from each of the prazosin–cocaine testing conditions.

2.1.5. Data analyses

The data files generated in each session for each squad of rats were in turn exported using the Versadat module

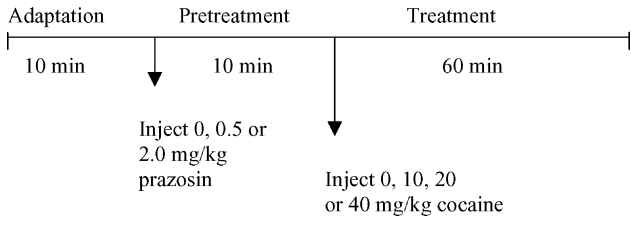

Fig. 1. Temporal summary of the adaptation, pretreatment, and treatment conditions of Experiment 1.

(Accuscan Instruments) to a spreadsheet for subsequent statistical analyses. The Versamax system provides a real-time summary of numerous measures of locomotor activity. Of these, the total distance traveled score (cm) is considered to be an important measure of locomotor activity (e.g. Sandberg et al., 1987). The total numbers of horizontal beam breaks (HACTV) plus vertical beam breaks (VACTV) were summated for each rat for each testing period in order to provide a composite locomotor measure that is comparable to the total vertical and horizontal beam breaks measure employed by Berthold et al. (1992). The present study also examined the impact of prazosin on stereotypy counts in order to further extend previous analyses which focused primarily on horizontal and vertical locomotion and because cocaine induces stereotypic movements, which can interfere with locomotion. In this system, stereotypy count is the number of times an animal breaks the same beam (or set of beams) and thus this gross stereotypy measure does not differentiate grooming or oral stereotypies related to licking or chewing. A final measure of this experiment was resting time (s).

The overall study design included the between-group factors of pretreatment (0, 0.5, or 2 mg/kg prazosin) and treatment (0, 10, 20, and 40 mg/kg cocaine) and a within-group factor of time after cocaine treatment (0–60 min in 5-min blocks). Separate simple-effects analyses of variance (ANOVAs) were computed for each dose of cocaine comparing differences between the prazosin groups in each dependent measure during the 5-min period (time = 0 in each panel) prior to cocaine administration. Because several of these analyses indicated a significant between-prazosin group difference (indicated by an * in each panel in Figs. 1–4), subsequent analyses used baseline scores at time = 0 as a covariate (hereafter referred to as ANCOVA). Separate analyses were computed (Systat 8.0; SPSS, Chicago, IL) for each cocaine dose for each dependent measure using a 3 (prazosin dose) × 12 (5-min test periods over 60 min) ANCOVA. Difference probabilities that were <0.05 were deemed to be statistically significant.

2.2. Experiment 2

2.2.1. Animals

The animals were 36 male Sprague–Dawley albino rats (obtained from Harlan Industries) weighing approximately 200–224 g at the beginning of the study. The rats were housed individually in standard wire-mesh hanging cages (24 × 20 × 18 cm) in a colony room maintained at 21.0 ± 1 °C under a 12:12 h illumination schedule (lights on at 0800 h). The rats were maintained on a chow pellet diet (Teklad #2001) and tap water in the home cage, except for during the 1-h ingestive tests, as described below.

2.2.2. Sweetened mash diet

A palatable mash diet consisting of 300 ml standard rat chow (Teklad), 200 ml tap water, and 50 ml sweetened condensed milk (Albertson's, Boise, ID) was prepared fresh daily and presented to the rats in separate Pyrex dishes (300 ml). This palatable mash diet is readily consumed by rats and generates relatively high baseline food intakes, thus allowing for the determination of drug-induced hypophagia without requiring prior food deprivation (Cooper, 1987). The energy density of the mash diet was calculated to be 2.77 kcal/g.

2.2.3. Drugs

A vehicle solution was prepared using sterile distilled water and 0.9% (w/v) sodium chloride. Solutions of cocaine hydrochloride (10, 20, or 40 mg/ml) and prazosin hydrochloride (1 and 2 mg/ml) were prepared in sterile distilled water prior to injection. All drugs were obtained from Sigma. Drug doses were calculated as the salt and all injections were administered i.p. at a volume of 1 ml/kg.

2.2.4. Procedure

The rats were maintained in the colony room for 5 days prior to the start of behavioral testing to acclimate them to colony maintenance procedures including daily weighing and handling.

Each rat underwent a series of seven baseline ingestive trials. Each 60-min trial started at about 0900 h and was conducted under full illumination in the home colony room. The start times for each rat were staggered in 1-min intervals to accommodate subsequent injection procedures. Rat body weights were recorded to the nearest g prior to each trial and each rat was then placed into a separate wire-mesh testing cage containing a weighed amount of the mash diet (in a glass dish) and a calibrated drinking tube containing tap water. Mash intakes were recorded to the nearest 0.1 g and were adjusted for any spillage collected on paper towels placed beneath each cage. Water intakes were recorded to the nearest 1 ml, but were not corrected for spillage. On days 5–7, the rats were adapted to the injection protocol by daily sham injections (i.p.) of 0.9% saline (1 ml/kg) administered at −20 and −10 min prior to the start of each ingestion trial. The data from these 3 baseline days were averaged for each rat and were used to form four groups ($n = 9$ each) of comparable average baseline food and water intake. Each of these groups was, in turn, randomly assigned to one of the four cocaine treatment (0, 10, 20, or 40 mg/kg) conditions.

On each of 3 drug test days, ingestive trials were conducted using the procedures described above. On each trial, the rats received a pretreatment injection of prazosin (0, 1, or 2 mg/kg) at −20 min, and then received a treatment injection of cocaine (0, 10, 20, or 40 mg/kg) at −10 min prior to the start of each ingestion trial. In this study, the timing of the cocaine injections (−10 min) ensured that the start of the ingestive trials occurred at about the time of peak cocaine action. The drug injections were staggered at 1-min intervals. At the end of the 60-min test period, food and water consumption were measured as

indicated above. Each rat always received the same treatment injection of cocaine, but a different pretreatment dose of prazosin on each of the 3 drug test days. The order of administration of prazosin doses was given randomly for each rat. Two inter-trial test days, in which eating and drinking were recorded without injections, were interposed between successive drug trials.

2.2.5. Data analyses

The overall design of the experiment included a between-group factor of cocaine dose (0, 10, 20, or 40 mg/kg) and a within-group factor of prazosin dose (0, 1, or 2 mg/kg). Linear-trend analyses (Kirk, 1982) of food intake were computed to assess the dose dependence of cocaine action on eating. Separate planned one-way analyses of variance were computed using Systat comparing differences among the prazosin groups, at each dose level of cocaine, for the dependent variables of food intake and water intake. Additional contrasts between group means were made using Tukey's procedure. Difference probabilities <0.05 were deemed to be statistically significant.

3. Results

3.1. Experiment 1

3.1.1. Total distance traveled scores

In this study, the rats were adapted to the activity chambers for 2 days prior to an assessment of the impact of prazosin and cocaine on locomotion. On the third day, rats pretreated with vehicle at time = – 2 and then treated with vehicle at time = 0 (Fig. 2A) exhibited a decline in total distance traveled scores over the test session. In contrast, administration of cocaine at doses of 10, 20, and 40 mg/kg in the 0 mg/kg prazosin groups produced dose-dependent increases in total distance traveled scores over the 60-min test period (compare 0 mg/kg prazosin groups in each of the panels A, B, C, and D in Fig. 2). Rats pretreated with 0 mg/kg prazosin and then treated with either 10 or 20 mg/kg cocaine exhibited a peak increase in total distance traveled scores at between 5 and 10 min after cocaine administration, and these scores returned to baseline by 60 min after injection. In contrast, total distance scores of rats pretreated with 0 mg/kg prazosin and then treated with 40 mg/

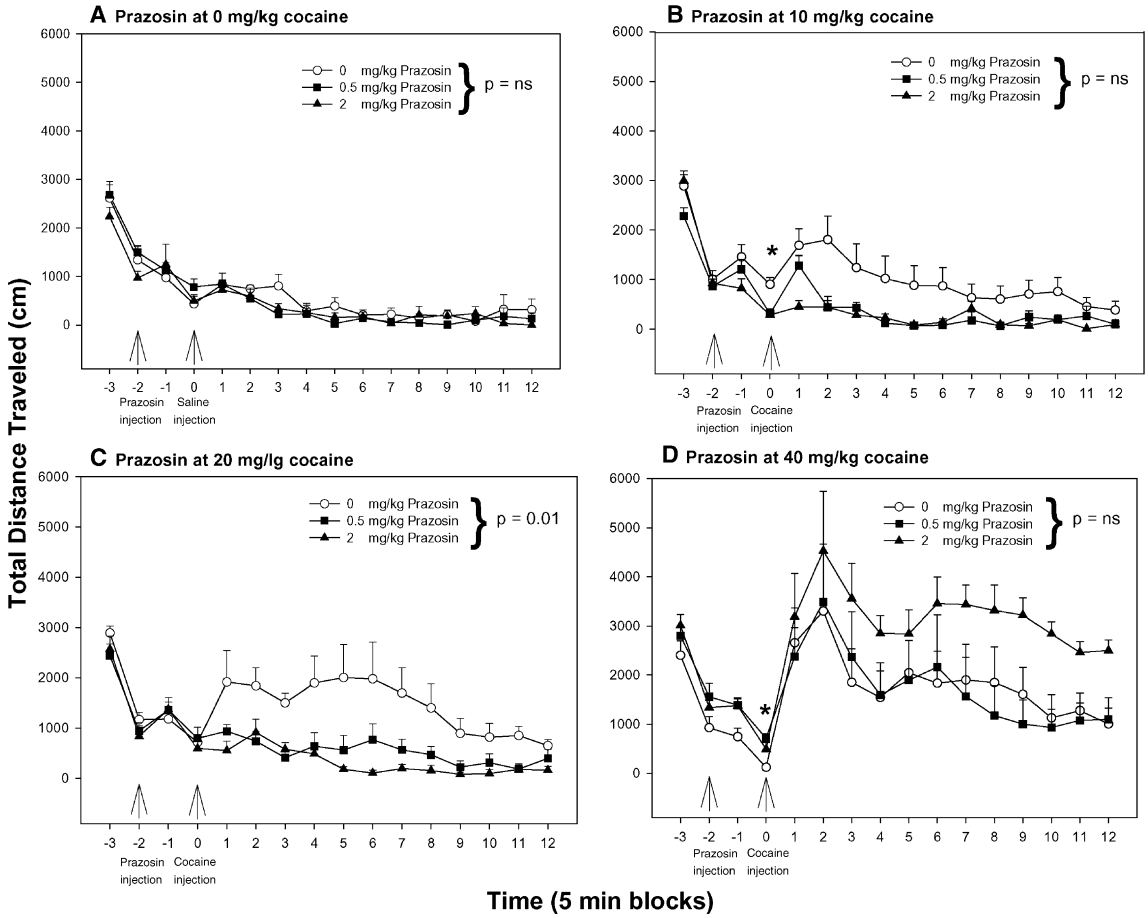

Fig. 2. Mean group total distance traveled scores (cm) in successive 5-min blocks during a 10-min baseline period (time = – 3 and – 2) during a 10-min period after injection with 0, 0.5, or 2.0 mg/kg prazosin (time = – 1 and 0) and during a 60-min period (time = 1–12) after injection with 0, 10, 20, or 40 mg/kg cocaine. Panels A, B, C, and D present the total distance traveled scores for rats injected at time = 0 with 0, 10, 20, or 40 mg/kg cocaine, respectively. The lines above each symbol represent the S.E.M. An asterisk indicates a significant difference between groups prior to injection with prazosin ($P<0.05$).

kg cocaine peaked at 10 min after cocaine injection, but did not return to baseline by the end of the 60-min test period.

Pretreatment with either 0.5 or 2.0 mg/kg prazosin alone did not reliably alter total distance traveled scores in the absence of cocaine (Fig. 2A). An ANCOVA comparing total distance traveled scores for rats pretreated with prazosin and then treated with 0 mg/kg cocaine revealed no significant main effect of prazosin administration ($P=0.17$), nor was there a significant interaction of prazosin dose with time after 0 mg/kg cocaine administration ($P=0.76$).

Rats pretreated with either dose of prazosin and then treated with 10 mg/kg cocaine exhibited smaller increases in total distance scores than did rats in the 0 mg/kg prazosin–10 mg/kg cocaine group. However, when these data were analyzed using the baseline scores at the time of cocaine injection (time = 0) as a covariate, there was no significant main effect of prazosin ($P=0.36$) nor was there a significant interaction between prazosin and time after cocaine treatment ($P=0.18$). Administration of 20 mg/kg cocaine (Fig. 2C) produced a significantly smaller increase in total distance traveled scores in rats pretreated with either 0.5 or 2.0 mg/kg prazosin, relative to rats pretreated with vehicle and then treated with 20 mg/kg cocaine. These differences were confirmed by a significant main effect of prazosin ($F(2,17)=6.26$, $P=0.01$). Subsequent contrasts revealed that although each prazosin dose (averaged across time points 1–12 in Fig. 2C) was significantly different from vehicle ($P<0.01$), these doses were not different from one another. Finally, administration of 40 mg/kg cocaine (Fig. 2D) produced an elevation of total distance traveled scores for each of the prazosin-pretreated groups. Although it appeared that the change evident in rats pretreated with 2 mg/kg prazosin was larger than of rats pretreated with either 0.5 or 0 mg/kg prazosin, there were no significant differences among the groups after adjustment of these data for the initial differences between prazosin groups at the time of cocaine administration ($P=0.06$).

3.1.2. Composite activity scores

Earlier studies of locomotion in rats after prazosin and cocaine utilized horizontal and vertical photo beam systems (Berthold et al., 1992), which report total beam breakages

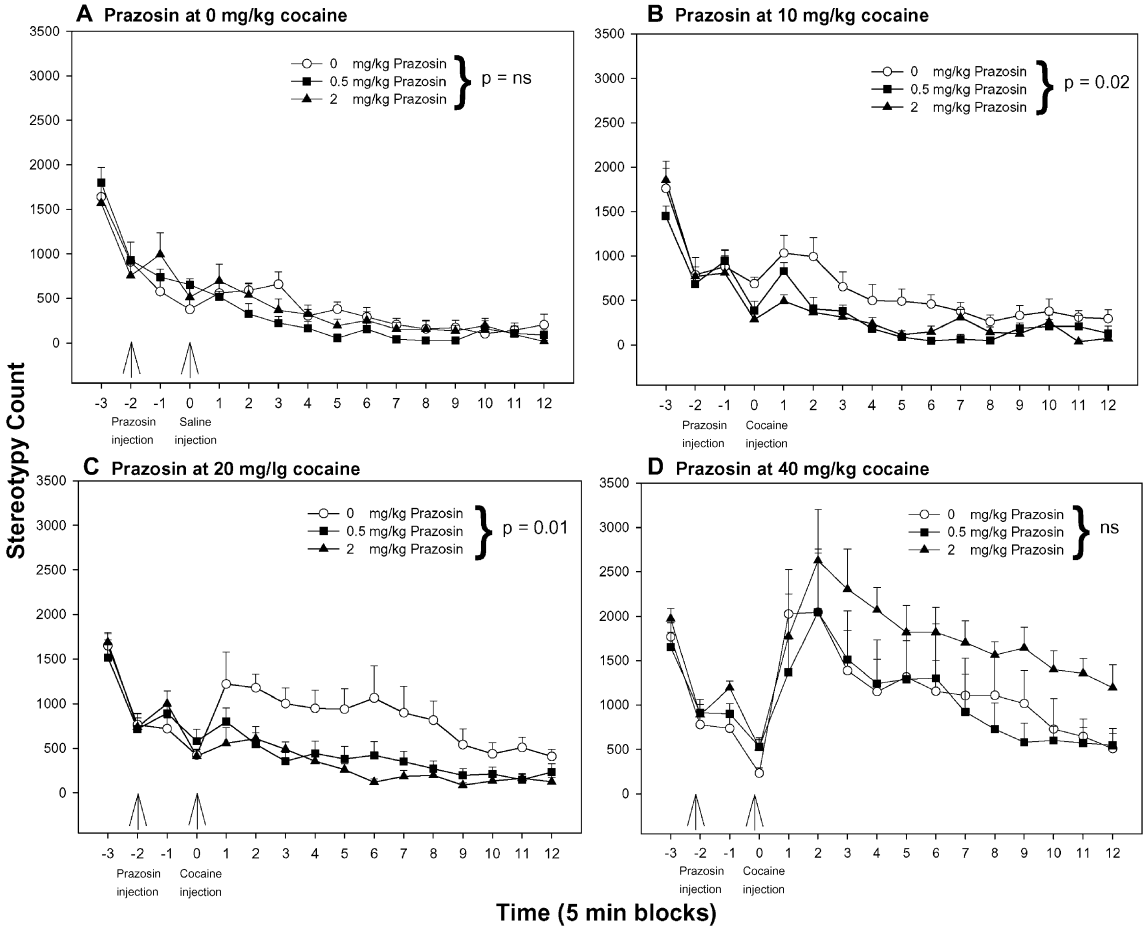

Fig. 3. Mean group stereotypy count scores in successive 5-min blocks during a 10-min baseline period (time = −3 and −2) during a 10-min period after injection with 0, 0.5, or 2.0 mg/kg prazosin (time = −1 and 0) and during a 60-min period (time = 1–12) after injection with 0, 10, 20, or 40 mg/kg cocaine. Panels A, B, C, and D present the stereotypy count scores for rats injected at time = 0 with either 0, 10, 20, or 40 mg/kg cocaine, respectively. The lines above each symbol represent the S.E.M. An asterisk indicates a significant difference between groups prior to injection with prazosin ($P<0.05$).

per unit time period. The composite activity score derived for the present study represents the sum, per 5-min period, of the horizontal activity plus vertical activity measures recorded using the Versamax system. The outcomes of this composite measure (data not depicted) were comparable to the outcomes noted using the total distance traveled scores presented above. Prazosin alone did not significantly alter the composite activity scores. Prazosin doses of 0.5 and 2.0 mg/kg produced significant attenuation of the impact of 10 and 20 mg/kg cocaine on composite activity scores (P's < 0.05). As was noted for the total distance traveled scores, administration of prazosin did not attenuate the stimulatory action of 40 mg/kg cocaine. Although there was a trend for the 2 mg/kg prazosin–40 mg/kg cocaine group to show greater elevation of composite activity scores relative to the other prazosin groups, these differences were not statistically significant ($P = 0.25$).

3.1.3. Stereotypy counts

Rats pretreated with vehicle and then treated with vehicle exhibited a gradual decline in stereotypy counts per time block over the test session (Fig. 3A). Prazosin administration in rats receiving 0 mg/kg cocaine (Fig. 3A) did not alter stereotypy counts. Rats pretreated with 0 mg/kg prazosin and then treated with 0, 10, 20, or 40 mg/kg cocaine exhibited dose-dependent increases in stereotypy counts (Fig. 3A–D). Rats pretreated with 0.5 or 2.0 mg/kg prazosin exhibited significantly smaller increases in stereotypy scores relative to rats pretreated with vehicle and then treated with either 10 mg/kg cocaine (Fig. 3B) ($F(2,17) = 4.80$, $P = 0.02$) or with 20 mg/kg cocaine (Fig. 3C) ($F(2,16) = 6.69$, $P = 0.01$). Neither 0.5 nor 2.0 mg/kg prazosin (Fig. 3D) significantly altered the stereotypy induced by 40 mg/kg cocaine ($P = 0.07$, $P = 0.54$).

3.1.4. Rest time

Over the 60-min test period, the rest scores gradually increased to a near maximal value of 300 s in rats treated with 0 mg/kg cocaine (Fig. 4A). There were no differences among the prazosin groups treated with 0 mg/kg cocaine (Fig. 4A). As expected, cocaine produced a dose-dependent reduction in rest time. The overall profile of the interactions

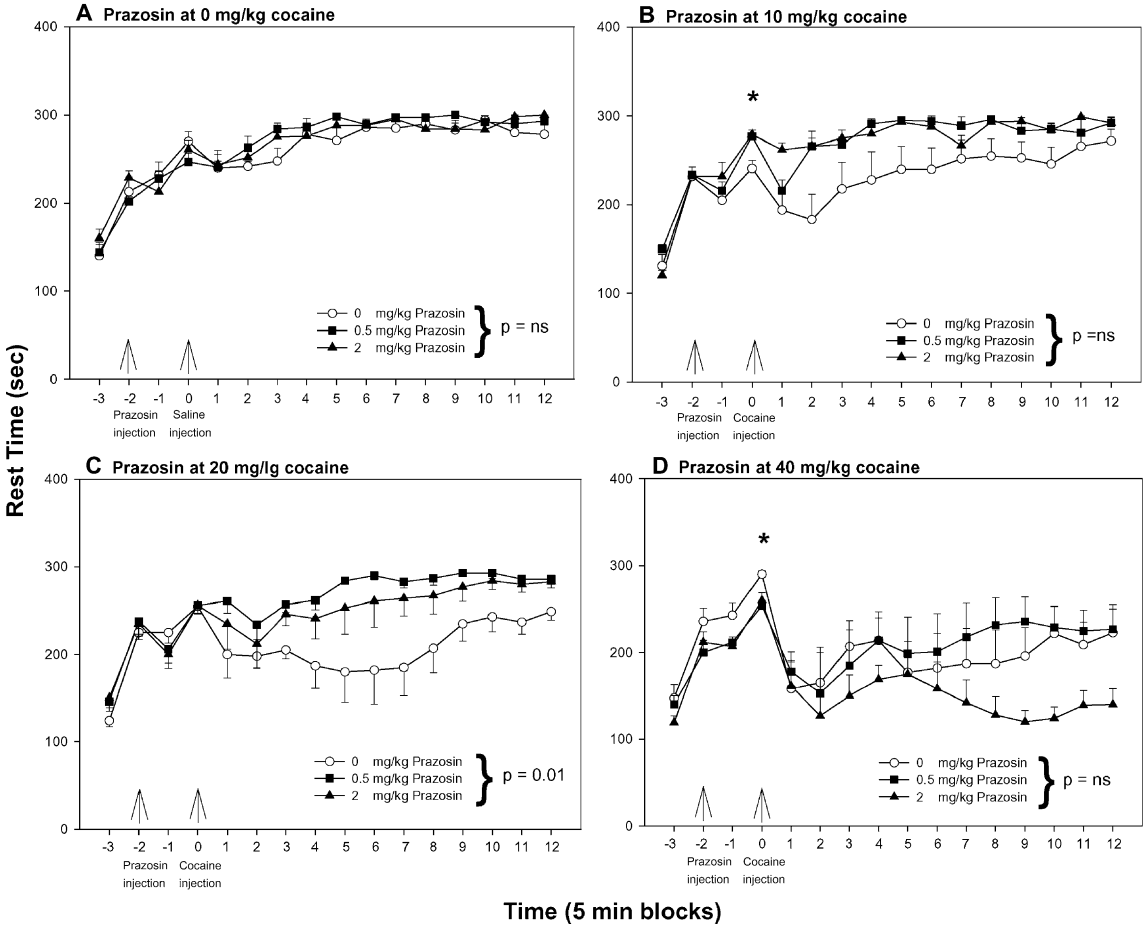

Fig. 4. Mean group rest time scores (s) in successive 5-min blocks during a 10-min baseline period (time = – 3 and – 2) during a 10-min period after injection with 0, 0.5, or 2.0 mg/kg prazosin (time = – 1 and 0) and during a 60-min period (time = 1–12) after injection with 0, 10, 20, or 40 mg/kg cocaine. Panels A, B, C, and D present the rest time scores for rats injected at time = 0 with either 0, 10, 20, or 40 mg/kg cocaine, respectively. The lines above and below each bar represent the S.E.M. An asterisk indicates a significant difference between groups prior to injection with prazosin ($P < 0.05$).

of prazosin with cocaine on rest time was inverted relative to other measures of locomotion (Fig. 4A–D). Specifically, prazosin significantly attenuated the inhibitory effect of 10 mg/kg cocaine ($F(2,17)=0.74$, $P=0.49$) and 20 mg/kg cocaine ($F(2,16)=6.14$, $P=0.01$) on rest time, but did not attenuate the action of 40 mg/kg cocaine on rest time ($P=0.23$).

3.2. Experiment 2

3.2.1. Food and water intake

The mash diet was readily consumed with intakes averaging nearly 8 g/60 min noted in rats pretreated with vehicle and then treated with vehicle. Administration of cocaine in rats pretreated with vehicle (0 mg/kg prazosin) produced a dose-dependent suppression of eating (Fig. 5: $F(3,32)=10.7$, $P=0.00005$). Trend analyses revealed a significant linear effect of cocaine on food intake ($F(1,32)=28.07$, $P<0.01$), but tests of higher order components were not significant. Pretreatment with prazosin only produced a slight, but nonsignificant, attenuation of the hypophagic action of 10 mg/kg cocaine ($P=0.34$). In contrast, prazosin significantly attenuated the hypophagic action of 20 mg/kg cocaine ($F(2,16)=4.14$, $P=0.04$). Subsequent contrasts for this dose of cocaine indicated that the prazosin doses were significantly different from prazosin vehicle, but were not different from each other. There was no significant effect of prazosin on the hypophagic action of 40 mg/kg cocaine ($P=0.64$). These effects of prazosin cannot be easily attributed to an action of prazosin on food intake per se, since administration of prazosin slightly, but not significantly, reduced food intakes in the 0 mg/kg cocaine group ($P=0.43$). Because the mash diet provided water in addition to food, the baseline water intakes in the present experiment averaged about 1 ml, a value that is at the threshold of measurement for this type of calibrated drinking tube. Although planned analyses of the water intake data indicated that administration of cocaine did not reliably suppress water intake ($P=0.44$), this outcome may reflect a floor value below which an inhibition of fluid intakes by cocaine cannot be reliably detected. Moreover, planned analyses indicated that prazosin alone did not significantly alter water intake in each of the cocaine treatment groups of this experiment ($P=0.07$).

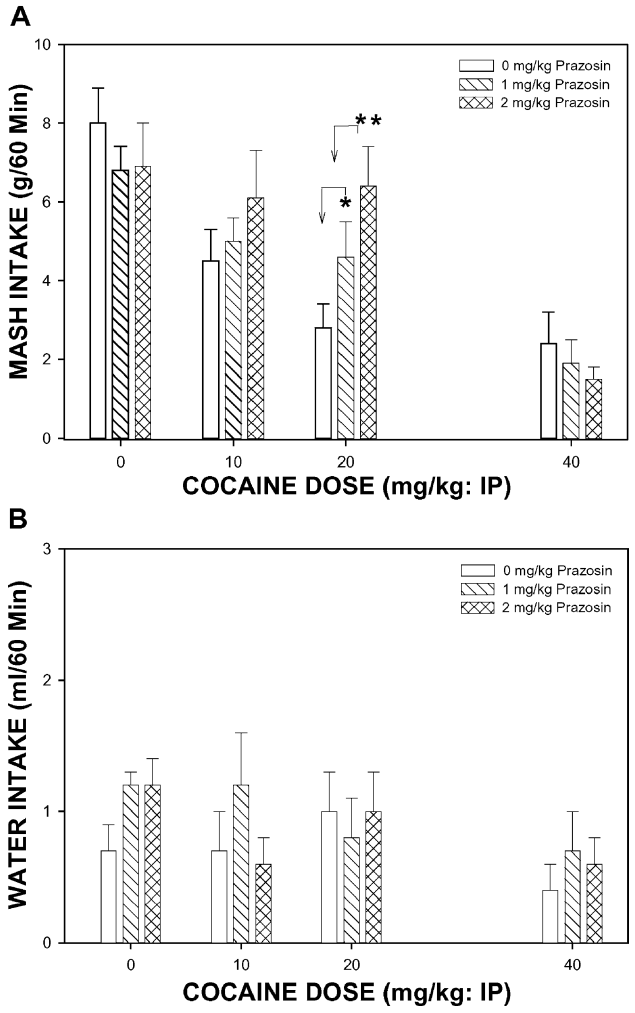

Fig. 5. Mean (±S.E.M.) group food intake (panel A) or water intake (panel B) during a 60-min period for rats pretreated (at −20 min) with 0, 1, or 2 mg/kg prazosin and then injected (at −10 min) with either 0, 10, 20, or 40 mg/kg cocaine. Asterisks denote a significant difference between a prazosin group relative to the 0 mg/kg prazosin control value (*$P<0.05$, **$P<0.001$).

4. Discussion

The present studies confirm that administration of the α_1-adrenoceptor antagonist prazosin significantly attenuated the behavioral actions of cocaine on locomotion and extended this effect of prazosin to the capacity of cocaine to inhibit eating in the rat. The results of Experiment 1 thus confirm earlier studies in which administration of prazosin significantly attenuated the locomotor stimulatory actions of cocaine (Berthold et al.,1992; Drouin et al., 2002a; Snoddy and Tessel, 1985). The current results may also be instructive with regard to the negative findings of Thiebot et al. (1981). In the present study, 0.5 mg/kg prazosin did not significantly attenuate the effects of 10 mg/kg cocaine in rats; the doses employed in the Thiebot et al. (1981) study (0.25 mg/kg prazosin versus 4 mg/kg cocaine) would not be expected to generate an antagonism of cocaine action in rats and would be less likely to be effective in mice given the typical dose differences that obtain between rats and mice.

The attenuation of cocaine effect by prazosin in the present study was not limited to horizontal locomotion. Cocaine was less effective in prazosin-pretreated rats in increasing total distance traveled scores as well as less effective in increasing stereotypy scores. The present study noted that prazosin was comparably effective at 0.5 mg/kg as well as 2.0 mg/kg; thus use of a higher prazosin dose did not confer greater attenuation of the behavioral actions induced

by 20 mg/kg cocaine. Moreover, the capacity of prazosin to attenuate cocaine action was limited to some, but not all doses of cocaine. For example, although these prazosin doses significantly attenuated the locomotor effects of 20 mg/kg cocaine, further increasing the cocaine dose to 40 mg/kg produced an enhanced degree of locomotor stimulation that was not attenuated by either prazosin dose. Similarly, prazosin was effective against a the hypophagic action of a narrow range of cocaine doses, i.e. prazosin significantly attenuated the effects of 20 mg/kg cocaine, but not that of the lower 10 mg/kg dose or the higher 40 mg/kg cocaine dose (Experiment 2). This pattern in which the behavioral actions of relatively high cocaine doses are refractory to receptor antagonism is not unique to the use of prazosin. Rapoza and Woolverton (1991), for example, reported that administration of Schering 23390, an antagonist of the dopamine D1 receptor, attenuated the hypophagic action of 16 mg/kg cocaine in rats, but failed to attenuate the hypophagic action of 32 mg/kg cocaine. There were no discernable actions of prazosin alone in the present study on locomotor or feeding behavior, suggesting that these doses of prazosin do not produce a general debilitation/facilitation of behavior.

Although changes in dopamine systems have been implicated in the locomotor stimulatory effects of cocaine, there are compelling studies linking changes in central norepinephrine, and consequent activation of α_1-adrenoceptors to locomotion generally and specifically to the action of cocaine on locomotion. Targeted deletion in mice of the membrane transporter for norepinephrine results in enhanced synaptic levels of norepinephrine and an exaggerated behavioral response to cocaine (Xu et al., 2000). Intracranial infusion of phenylephrine, an α_1-adrenoceptor agonist, produced locomotor activation in mice and rats, but not in animals pretreated with the α_1-adrenoceptor antagonist prazosin (Clineschmidt et al., 1979; Heal, 1984). Moreover, infusions of α_1-antagonists alone directly into mouse brain suppress locomotor behavior (Stone et al., 1999). Three subtypes of α_1-adrenoceptors—α_{1A}, α_{1B}, and α_{1D}—have been identified in brain (Domyancic and Morilak, 1997; Rokosh et al., 1994). Of these, the α_{1B} and perhaps α_{1A} subtypes have been linked to the capacity of norepinephrine to facilitate locomotor behavior (Stone et al., 2001; Wada et al., 1997). Whether one or more of these α_1-adrenoceptor subtypes play a role in the capacity of cocaine to stimulate locomotion in the rat is unknown.

Comparatively few studies have examined the hypophagic action of cocaine, and even fewer studies have sought to characterize the neurochemical/pharmacological substrates by which cocaine induces hypophagia. Administration of cocaine acutely inhibits eating in rats (Balapole et al., 1979; Bedford et al., 1980; Blavet and DeFeudis, 1982; Wilson and Brenkert, 1978), perhaps by delaying the onset of eating and by reducing meal frequency (Cooper and van der Hoek, 1993). In contrast, chronic administration of cocaine may result in hypophagic tolerance (Giorgetti and Zhdanova, 2000), and withdrawal from chronic cocaine increases eating in some (e.g. Carroll and Lac, 1987), but not all (e.g. Fung and Richard, 1994) studies. The hypophagic action of cocaine is evident in nonhuman primates (Foltin et al., 1990). Interestingly, human addicts report using cocaine to reduce their appetite and to control their body weight and more women than men report this use of cocaine (Cochrane et al., 1998; Jonas et al., 1987).

As was the case for locomotion, the hypophagic actions of cocaine have been related to the capacity of cocaine to increase dopamine neurotransmission. Cocaine increases synaptic dopamine levels (Hernandez and Hoebel, 1988), which can inhibit eating when localized within the lateral hypothalamus (Leibowitz and Rossakis, 1979). Importantly, antagonism of postsynaptic dopamine receptors attenuates cocaine-induced hypophagia (Heffner et al., 1977; Rapoza and Woolverton, 1991). While some dopamine antagonist drugs also exert antagonist actions at α_1-adrenoceptors (Richelson and Souder, 2000), the present studies document a significant involvement of brain norepinephrine systems and α_1-adrenoceptors in the mediation of cocaine-induced hypophagia. Inactivation of α_1-adrenoceptors by prazosin attenuated the hypophagic action of cocaine (Experiment 2), and the overall profile of these effects resembled that noted in Experiment 1 for cocaine-stimulated locomotion. Prazosin was significantly effective against a narrow range of cocaine doses (20 mg/kg cocaine, but not against the lower 10 mg/kg or the higher dose of 40 mg/kg cocaine). Cocaine only slightly reduced water intake at 40 mg/kg and it should be noted that water intakes were negligible in this experiment because the mash diet contained water. It remains possible that prazosin may attenuate the hypodipsic action generated by cocaine in studies in which baseline water intakes alone are higher and are monitored in a testing situation that only involves drinking.

Sympathomimetic drugs may alter eating, in part, because these drugs alter motor function which interferes with eating (Halford et al., 1998). In the present study, cocaine induced hyperlocomotion and hypophagia and these effects were attenuated by prazosin. The effects of prazosin, however, are not likely due to a general change in motoric function (e.g. Stone et al., 2001) in that increases in eating (but not drinking) were noted in cocaine-treated rats pretreated with prazosin, whereas prazosin alone did not reliably alter locomotion or eating behavior in the rat. Moreover, prazosin has been shown in other studies to attenuate the hypophagic action of sibutramine (Jackson et al., 1997a), a drug that acts to block reuptake of norepinephrine and of 5-HT without inducing behavioral arousal.

Hypophagia is a reliable finding that accompanies administration in rats of a variety of drugs that are agonists at the α_1-adrenoceptor (cf. Wellman et al., 1993). The report of weight gain following chronic use of α_1-adrenoceptor antagonists in humans (Bray, 2000) suggests that activation of these receptors functions in humans to inhibit eating. Indeed, antagonism of α_1-adrenoceptors by prazosin reverses or strongly attenuates the hypophagic action of a variety of

drugs that are direct agonists at the α_1-adrenoceptor (e.g. phenylpropanolamine: Wellman et al., 1993) or that indirectly activate α_1-adrenoceptors by inhibiting the norepinephrine transporter (e.g. aminorex, phentermine, ephedrine, and sibutramine: Jackson et al., 1997a; Wellman et al., 2003, in press). The present study extends that latter line of research by confirming that cocaine-induced hypophagia in rats is critically dependent on activation by norepinephrine of α_1-adrenoceptors.

The recognition that prazosin attenuates the capacity of cocaine to alter eating and locomotion raises the question as to whether these findings reflect a general pharmacological action of prazosin that cuts across behavioral systems that are primarily controlled by dopamine neurons and that may be facilitated by noradrenergic inputs (Piascik and Perez, 2001). Application of dopamine or of α_1-adrenoceptor agonists such as phenylephrine produces excitation of rat spinal cord motor neurons (Wada et al., 1997) and of cells within the substantia nigra (Berretta et al., 2000). Prazosin administration blocks the excitation produced by α_1-adrenoceptor agonists and is known to alter the firing pattern of ventral tegmental dopamine neurons (Grenhoff and Svensson, 1993). Although prazosin attenuates the behavioral actions of cocaine (e.g. locomotion and hypophagia), Woolverton (1987) reported that prazosin had no significant effect on cocaine-associated reward. Yet, deletion of the α_{1B}-adrenoceptor subtype in mice resulted in an attenuation of the capacity of cocaine to induce locomotion and to produce conditioned place preference (Drouin et al., 2002b). The failure of prazosin to alter cocaine reward in the Woolverton (1987) study may relate to separate neural circuits for reward versus eating/locomotion (Carelli et al., 2000) or may reflect other critical differences between the testing paradigms used to examine feeding/locomotion versus reward (e.g. species, method used to inactivate α_1-adrenoceptors, and/or prior experience with cocaine).

Finally, multiple brain regions have been shown to contain α_1-adrenoceptors, including hypothalamic sites that modulate eating as well as sites involved in the control of locomotion (Leibowitz et al., 1982; Young and Kuhar, 1980). Although mRNAs for each of the α_1-adrenoceptor subtypes have been identified within the PVN and other feeding-relevant sites (e.g. Domyancic and Morilak, 1997; Rokosh et al., 1994), it is currently unclear as to which of these α_1-adrenoceptor subtypes may contribute to the inhibition of eating in general or to the capacity of cocaine to inhibit eating. Of interest will be the subsequent determination of whether a common α_1-adrenoceptor subtype contributes to the capacity of cocaine to enhance locomotion, induce reward and inhibit eating.

Acknowledgements

This research was supported in part by funds provided by a grant from the Tobacco Health Initiative to LLB, PJW, and ACB, and from NIDA to JRN. The experiments reported herein were approved by the Texas A&M University Laboratory Animal Care Committee.

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