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Tyrosine Pretreatment Alleviates Suppression of Schedule-Controlled Responding Produced by Corticotropin Releasing Factor (CRF) in Rats

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AHLERS, S. T., M. K. SALANDER, D. SHURTLEFF AND J. R. THOMAS. *Tyrosine pretreatment alleviates suppression of schedule-controlled responding produced by corticotropin releasing factor (CRF) in rats.* BRAIN RES BULL **29**(5) 567–571, 1992.—Disruption of performance observed when animals are exposed to physical stressors which deplete brain catecholamines can be alleviated by pretreatment with the catecholamine precursor tyrosine. Central administration of the stress hormone corticotropin releasing factor (CRF) has been shown to affect a variety of behaviors and also to potently increase the release of central catecholamines. Since CRF-induced disruption of behavior may involve CRF-induced depletion of brain catecholamines, the present study examined whether tyrosine would alleviate suppression of schedule-controlled responding in rats resulting from ICV administration of CRF. Administration of CRF (1.0 μg–10 μg) produced dose-dependent suppression of response rate and total number of earned reinforcers in rats responding on a multiple fixed-interval 60 s/fixed-ratio 20 schedule for food reinforcement. Pretreatment with 200 mg/kg tyrosine (IP) administered with ICV saline decreased response rate but did not lower total reinforcers, whereas 400 mg/kg of tyrosine decreased both. Injection of 400 mg/kg tyrosine reduced, but did not completely restore, CRF-induced suppression of behavior. The 200 mg/kg tyrosine dose was less effective in alleviating CRF-induced suppression of performance. These data indicate that pretreatment with the catecholamine precursor tyrosine can partially ameliorate performance decrements resulting from CRF administration.

Corticotropin releasing factor Precursor Tyrosine Norepinephrine Dopamine Stress Schedule-controlled behavior

CORTICOTROPIN releasing factor (CRF) has been shown to influence a variety of biochemical, physiological, and behavioral processes thought to reflect the cascade of events activated during acute stress. In addition to its role in promoting the release of adrenocorticotropin hormone (ACTH) and adrenocorticoids through the pituitary/adrenocortical axis, administration of CRF has been shown to produce many of the concomitant physiological and behavioral changes observed when animals are exposed to a variety of aversive and/or stressful conditions [see (12) and (27) for review]. The observation that many of the behavioral effects produced by CRF administration are unaffected by pretreatment with dexamethasone or hypophysectomy (6) suggests that the effects of CRF on behavior are not mediated through the hypothalamic-pituitary-adrenal (HPA) axis.

Administration of CRF into the lateral ventricles has been shown to increase the release of the central catecholamines dopamine (DA) and norepinephrine (NE) (3,11,21,22). Evidence suggests that some of the behavioral effects observed after central administration of CRF are due to increased catecholamine neurotransmission, particularly NE. For example, infusion of CRF onto locus coeruleus neurons increases their firing rate (34,35) and also produces anxiogenic and locomotor effects that are similar to those observed with intraventricular administration (8). Further implication of noradrenergic pathways in the effects of CRF on behavior are shown by studies in which CRF effects are blocked by noradrenergic drugs. For example, β-adrenergic antagonists block CRF-induced suppression of responding in a conditioned-emotional response (CER) paradigm (9) as well as CRF-induced increases in defensive withdrawal (38,39). Increases in locomotor activity produced by CRF are inhibited by the α-adrenergic receptor antagonists phentolamine and yohimbine (17). Adrenergic modulation has also been indicated by the finding that inhibition of gastric secretion observed with central administration of CRF is blocked when NE is depleted with DSP4 (1). Although CRF potently increases DA release, the evidence for dopamine (DA) involvement in the behavioral actions of CRF is mixed. Suggestions that CRF-induced increase in DA activity may influence behavior has been shown by Cole and Koob, who demonstrated that CRF potentiates amphetamine-induced stereotyped behavior in the rat (10). On the other hand, administration of DA antagonists (18,19) or depletion of DA with 6-hydroxydopamine (6-OH-DA) (33) are ineffective in

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blocking the effects of CRF on locomotor activity. For this reason, the modulatory role of increased DA neurotransmission in the behavioral actions of CRF are uncertain.

Stress-induced impairments in performance may stem from excess release and subsequent depletion of catecholamines. For example, exposure to tail-shock stress causes depletion of NE in several brain areas and also leads to decreased locomotor activity and exploratory behavior in an open field (4,20,30,31,36). Administration of the catecholamine precursor tyrosine in the diet, or by injection just prior to testing, has been shown to block depletion of NE as well as the reduction in exploratory and locomotor activity resulting from exposure to various physical stressors (4,20,30,31). Alleviation of specific behavioral deficits have also been observed in that tyrosine has been shown to improve performance on cognitive and reaction time tests in humans exposed to a combination of high altitude and cold stress (2).

Since excess release of central catecholamines has been implicated in the behavioral effects of CRF, it is possible that some of the behavioral changes resulting from CRF administration may be due to depletion of brain catecholamines. Accordingly, the aim of the present study was to determine whether suppression of schedule-controlled behavior on a multiple schedule with CRF in rats would be affected by pretreating subjects with tyrosine. The effects of tyrosine on CRF were measured using schedule-controlled behavior which has previously been shown to be suppressed by central administration of CRF (3,5,7,13,14,28).

METHOD

Subjects

Six Long–Evans rats maintained at 85% of their free feeding body weight of approximately 325 g served as subjects. Rats were individually housed in hanging cages in an air controlled unit. Water was available continuously in the home cage.

Apparatus

The subjects performed in a standard two-lever operant chamber 24.1 × 30.4 × 26.6 cm. Two response levers were mounted on the front wall, 5.0 cm above the grid floor and 3.8 cm from either of the side walls. A food tray was mounted 1.2 cm above the grid floor and in the center of the front wall equidistant from each of the levers. The tray was connected by a short tube to a pellet feeder located behind the front wall which could dispense 45 mg (Bio-Serv. Inc., Frenchtown, NJ) food pellets. A small light with a white lens cover was mounted 5.0 cm above both the right and left levers. A house light was mounted on the top of the front wall. The experimental chamber was placed within a larger sound- and light-attenuating enclosure that was provided with white noise to mask extraneous sounds and a fan for adequate ventilation. Experimental events were controlled and recorded by a microcomputer system.

Procedure

Animals were trained to lever press for food presentation by the method of successive approximations. Once lever-pressing behavior was established, rats were gradually shaped to respond on a multiple schedule of reinforcement with a fixed ratio (FR) 20 schedule on the left lever and a fixed interval (FI) 60 s schedule on the right lever. In the FR20 schedule, the 20th response produced food presentation. In the FI60 schedule, the first response after 60 s produced the food reward. A light located directly above each lever was illuminated when the respective schedules were operative. During a daily session, consisting of exposure to 10 components each of the two schedules, the components alternated regularly, starting with the FI schedule, and were separated by a 30-s period during which all lights were extinguished and lever pressing had no scheduled consequences (timeout). Each schedule component was required to be completed within a 2-min period (limited hold); if the schedule requirement was not met within that time, the component terminated and the schedule alternated into the next component in the session after the 30-s timeout. Sessions were conducted 5 days per week (M–F).

Surgical Procedure

Once stable performance on the multiple schedule was reached and maintained for several weeks, rats were implanted with a chronic cannula placed into the lateral ventricle. Rats were anesthetized with pentobarbital sodium (50.0 mg/kg, IP) and were placed in a stereotaxic apparatus. A 22 gauge guide cannula (Plastics One, Roanoke, VA) was implanted into the lateral ventricle using the following coordinates: AP = −0.8; L = +1.3, from bregma using stereotaxic coordinates from Paxinos and Watson (29). The depth or vertical location of the cannula was determined individually with each rat based upon a sudden drop in the fluid level (phosphate-buffered saline solution, Sigma, St. Louis, MO) in a piece of 20 cm tubing attached to the guide cannula as it was being slowly lowered into the ventricle. The guide cannula was anchored in place by cranioplastic cement which surrounded the guide cannula and four stainless steel screws threaded into the skull. At all times other than during injection, the guide cannula was sealed with a dummy cannula to maintain patency (Plastics One, Roanoke, VA). Drug studies were undertaken no sooner than 2 weeks after implantation of the cannula.

Drug Administration

CRF (Peninsula Laboratories, San Carlos, CA), and tyrosine methyl ester HCl (Sigma, St. Louis, MO) were dissolved in sterile 0.9% saline and were injected as freshly prepared solutions. Tyrosine was administered into the peritoneal cavity (IP) in a volume of 1.0 ml/kg body weight. CRF or saline was injected intracerbroventricularly (ICV) through a 28 gauge injector cannula that, when inserted, extended 1 mm beyond the tip of the guide cannula into the ventricle. The injector cannula was connected to a Hamilton microliter syringe (Reno, NV) with approximately 30 cm of polyethylene tubing. A Harvard microsyringe pump (Model 22, South Natick, MA) was programmed to deliver the solution through the injector at a flow rate of 10 μl/min. Injections of saline or CRF (1.0, 3.0, or 10 μg) were given in a volume of 5 μl 60 min before the session. Tyrosine was administered systemically in a concentration of either 200 or 400 mg/kg body weight 90 min before the session or 30 min prior to central administration of CRF or saline. CRF, saline, and tyrosine pretreatment combinations were administered in a mixed sequence. Drugs were administered on Tuesdays and Fridays. During other days of the week the subjects performed on the multiple schedule baseline.

Data Analysis

Overall group differences were determined by analysis of variance (ANOVA) with repeated measures. Pairwise comparisons were accomplished using a paired *t*-test (one-tailed).

RESULTS

Response Rate

CRF produced dose-dependent suppression of response rate in the FI, $F(3, 15) = 22.46$, $p < 0.001$, and FR, $F(3, 15) = 34.99$, $p < 0.001$, components as shown in the left and right panels in Fig. 1, respectively. In both components, 1.0 μg CRF decreased response rates by approximately 50%, whereas the 3.0 μg and 10.0 μg doses produced progressively more suppression. Analysis of response rate in the FI component indicated a nonsignificant main effect of tyrosine pretreatment, $F(2, 10) = 2.32$, $p > 1.0$. However, there was a highly significant interaction between tyrosine and CRF, $F(6, 30) = 4.71$, $p < 0.002$, which resulted from the alleviation of the rate-decreasing effects of high doses of CRF and the rate-decreasing effects of tyrosine administered with ICV saline. Pairwise analysis indicated a significant reduction of CRF-induced suppressed responding with 400 mg/kg tyrosine in combination with 3.0 μg, $t = 3.43$, $p < 0.02$, and 10.0 μg, $t(5) = 2.53$, $p < 0.05$ CRF. Although 400 mg/kg tyrosine increased the rate of responding when administered in combination with 1.0 μg CRF, this did not reach statistical significance. Analysis also indicated that 200 mg/kg, $t(5) = 3.19$, $p < 0.05$, and 400 mg/kg, $t(5) = 3.15$, $p < 0.05$, tyrosine significantly decreased response rate when it was given in combination with ICV saline.

In the FR component, the overall pattern was similar in that there was a nonsignificant tyrosine treatment main effect and significant CRF treatment by tyrosine interaction, $F(6, 30) = 6.22$, $p < 0.001$. Injection of 200 mg/kg, $t(5) = 2.69$, $p < 0.05$, and 400 mg/kg, $t(5) = 4.01$, $p < 0.01$, tyrosine in combination with ICV saline decreased FR response rate. Pairwise analysis indicated that 400 mg/kg of tyrosine significantly attenuated suppression of responding observed after administration of 10.0 μg CRF, $t(5) = 2.14$, $p < 0.01$.

Earned Reinforcers

Analysis of the effects of CRF alone revealed that CRF produced dose-dependent suppression of the number of FI, $F(3, 15) = 9.35$, $p < 0.001$, and FR, $F(3, 15) = 14.24$, $p < 0.001$, reinforcers obtained (Fig. 2). In both the FI and FR components, 1.0 μg CRF produced a nonsignificant decrease in total reinforcers earned. The 3.0 μg dose of CRF decreased total reinforcers in both components to approximately 60% of control. At the 10 μg CRF dose, rats obtained approximately four out of 10 reinforcers when the FI schedule was imposed and approximately two reinforcers when the FR schedule of reinforcement was active.

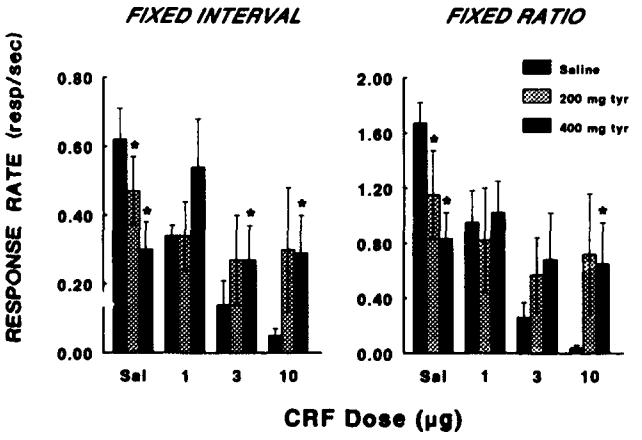

FIG. 1. Dose–response curves showing mean response rate (±SEM) during performance on the multiple FI/FR schedule. CRF or saline were administered (ICV) 60 min prior to the session. Systemic injections of saline or tyrosine (200 or 400 mg/kg, IP) were administered 90 min before the session or 30 min prior to central administration of CRF or saline. *$p < 0.05$ from the corresponding saline injected control condition.

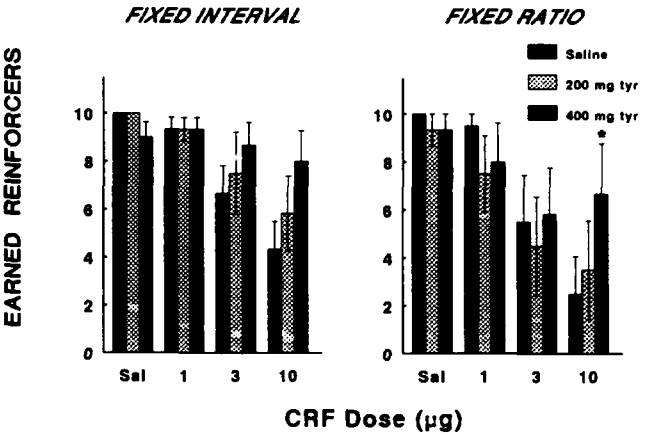

FIG. 2. Dose–response curves showing the mean total number of reinforcers earned (±SEM) in each component of the multiple FI/FR schedule. A maximum of 10 FI and 10 FR reinforcers could be earned within a session. *$p < 0.05$ from the corresponding saline injected control condition.

Significant tyrosine and CRF interactions for the FI, $F(6, 30) = 5.91$, $p < 0.001$, and FR, $F(6, 30) = 4.54$, $p < 0.002$, components were accompanied by nonsignificant main effects of tyrosine during the FI, $F(2, 10) = 0.36$, $p > 1.0$, and FR, $F(2, 10) = 2.61$, $p > 1.0$, schedules. Individual comparisons indicated that while 400 mg/kg tyrosine increased the total number of earned reinforcers after administration of 10 μg CRF, the effect was only statistically significant in the FR component, $t(5) = 2.21$, $p < 0.05$.

DISCUSSION

CRF produced dose-dependent suppression of responding on the multiple FI/FR schedule that was partially alleviated by pretreatment with tyrosine. The effects of CRF and tyrosine administration, alone and in combination, were similar across both the FI and FR components, suggesting that their effects were not schedule- or rate-dependent. Administration of tyrosine also produced nonspecific decreases in responding when administered with ICV saline. Tyrosine was most beneficial in combination with doses of CRF that produced the greatest rate-decreasing effects in both components of the multiple schedule.

Although response rate was suppressed in both the FI and FR components after administration of 1.0 μg CRF, there tended to be a more substantial decrease in the number of earned reinforcers in the FR component. Even so, rats were still able to complete the ratio requirements of each schedule within the 2-min limited hold, and were thus able to obtain the food reinforcer. The effects of 1.0 μg CRF on behavior, and in the FI component in particular, are similar to the effects of 1.0 μg of CRF in rats trained on a differential-reinforcement-of-low-rate (DRL) schedule as demonstrated by Britton and Koob (7). In that study, CRF-induced decreases in response rate were observed in the absence of a change in the rate of reinforcement. At the 3.0 μg and 10.0 μg CRF doses the reduction in response rates

were associated with reductions in reinforcers. The overall results of CRF on FI and FR responding are consistent with previous findings demonstrating decreases in schedule-controlled behavior with CRF that are not largely schedule- or rate-dependent (3,13,14).

The 200 mg/kg dose of tyrosine significantly decreased response rate in both components. Despite the drop in overall rate of responding, total reinforcers earned in the FI component was unaffected by 200 mg/kg tyrosine. A slight, but nonsignificant, decrease in total reinforcers was observed in the FR component. The decrease in response rate observed with 400 mg/kg tyrosine was associated with a significant reduction in reinforcers earned. Even though tyrosine decreased response rate in both schedule components, rats were only marginally affected in terms of completing the schedule requirements. These data suggest that decreases in the rate of responding are not due to an anorexigenic effect and are consistent with a previous report demonstrating that acute administration of tyrosine does not decrease food intake (16). In situations that do not explicitly involve appetitive behavior, tyrosine has been shown to slightly decrease (20,31), or have no affect (24), on locomotor activity. The effects of tyrosine on response rate may reflect a nonspecific decrease in activity.

Administration of tyrosine partially attenuated the suppression of response rate produced by CRF in both components of the multiple schedule. The effects of tyrosine were dose dependent in that the greatest reduction of CRF-induced suppression of responding was observed with 400 mg/kg tyrosine at the 3.0 μg and 10.0 μg doses of CRF. These were doses of CRF where responding was profoundly suppressed below control levels. There were no differences in sensitivity in either of the components in terms of tyrosine alleviation of CRF-induced suppression of responding.

The beneficial effects of tyrosine in the present study are consistent with previous reports in which tyrosine either reduced or completely blocked the behavioral effects of stress (2,4,20,30,31). This would suggest that CRF-induced suppression of responding may be the result of depletion of catecholamine neurotransmitter which is restored by increasing the availability of the precursor. However, since brain levels of tyrosine and catecholamines were not measured in this experiment, the precise mechanism of action of tyrosine on CRF-induced responding must await further analysis of catecholamines. When exposed to shock or cold stress, previous studies have shown depletion of NE was observed within 60 min (20,31,36). These findings suggest that it is possible that CRF stimulation of catecholamine release could deplete stores within the 1-h pretreatment interval utilized in the present study.

Still another important caveat is that the present data do not provide an unequivocal indicant of which catecholamine system is affected by tyrosine pretreatment. Recent findings by Westerink and De Vries (37) would appear to suggest that DA systems are not affected by preloading with tyrosine. Using in vivo microdialysis in awake animals they showed that a single 250 mg/kg injection of tyrosine had no effect on striatal DA release under basal conditions or when DA release was stimulated with haloperidol. Since previous data showing that CRF-induced behavioral changes are not affected by DA antagonists or depletion of DA with 6-OH-DA, these results would suggest that DA is not involved in tyrosine attenuation of suppressed responding with CRF. However, Olianas and Onali (26) have shown that CRF can stimulate DA synthesis in the striatum, possibly by direct receptor specific interaction with tyrosine hydroxylase. Thus, alleviation of CRF with tyrosine may result from an affect of the DA system under conditions in which CRF has directly increased synthesis of DA. Clearly, further study of the neural mechanisms which underlie the alleviation of CRF-induced suppression of responding with tyrosine is needed.

The majority of previous research demonstrating alleviation of behavioral impairment following exposure to physical stressors with tyrosine has focused attention on NE depletion. To a large extent this is due to the fact that extended exposure to inescapable shock that decreases motor activity is correlated with depletion of NE but not DA (36). Given the paucity of data showing DA modulation and the proven effectiveness of NE antagonists (9,17,38,39) and NE depletion (1) in blocking the effects of CRF, the alleviation of CRF-induced suppression of operant responding with tyrosine would appear to result from modulation of the NE system. In this regard, it is important to note that depletion of NE (31,35) and increased levels of CRF in cerebrospinal fluid (15,25) have been implicated in the pathogenesis of depression. The hypersecretion of CRF which is observed in clinically depressed patients may lead to excess release and eventual depletion of NE.

Because CRF has been shown to decrease food intake (23), it has been suggested that the apparent nonspecific decreases in operant responding across a variety of situations in which animals respond for food reinforcement are due to CRF-induced anorexia (13,14). Though suppression of response rate may be due to anorexia, the attenuation of CRF-induced suppression of responding with tyrosine is not easily explained as a reduction in an anoretic response. Indeed, a recent experiment by Hull and Maher (16) demonstrated that tyrosine potentiates anorexia produced by phenylpropanolamine, ephedrine, or amphetamine. Were CRF-induced suppression of responding in the present experiment due to an anoretic effect modulated through the release of catecholamines, then tyrosine should exacerbate the effects of CRF, not decrease it.

Although the mechanism whereby pretreatment with tyrosine alleviates CRF-induced suppression of responding are not fully clear, the present findings are nonetheless consistent with the hypothesis that tyrosine can alleviate stress-induced performance decrements. The data presented here extend these findings to include the reduction of a behavioral deficit produced by central administration of CRF on schedule-controlled behavior.

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