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Brain Amines and Effects of Chlordiazepoxide on Motor Activity in Response to Stress

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FREEMAN, G. B. AND J. B. THURMOND. *Brain amines and effects of chlordiazepoxide on motor activity in response to stress.* PHARMACOL BIOCHEM BEHAV 22(5) 665–670, 1985.—The effect of chlordiazepoxide (CDP) on emotional responsiveness to stress was determined in CD-1 male mice. The relationship of the monoamines to the mediation of emotional behavior was examined with drugs having selective actions on serotonin (5-HT), norepinephrine (NE), and dopamine (DA). Emotional behavior as measured by locomotor activity was increased by stress. This activation enhanced the stimulatory effect of low doses of CDP (5 and 10 mg/kg) and attenuated the depressant action of higher doses (20 and 40 mg/kg). Quipazine (0.5 mg/kg) reduced the depressant effect of CDP in stressed animals. Its action failed to support a proposed anti-serotonergic action of CDP and implicated possible dopaminergic involvement. In stressed mice, apomorphine (0.5 mg/kg) and clonidine (0.1 mg/kg) antagonized the stimulatory action of low doses of CDP. Behavioral effects of clonidine provide support for the notion that the stimulatory effects of CDP may be due to enhanced catecholamine (CA) neurotransmission. Whole brain levels of NE and DA were significantly increased when clonidine was combined with CDP. This indicated a possible reduction in CA turnover and activity.

Chlordiazepoxide Emotional responsiveness Locomotor activity Norepinephrine Dopamine Serotonin Clonidine Apomorphine Quipazine

THE activity of the hypothalamic-pituitary-adrenal system as an index of an animal's reaction to stress has been shown to be sensitive to differences in the intensity of psychological stimulation to which an animal is subjected [4, 17, 31]. Results showing that corticosterone (CS) levels correspond to differences in the degree of environmental change experienced by an animal lend support to the notion that psychological factors may be as important as physical stressors in regulating adrenocortical response [11,28].

Attempts have been made to identify or isolate a specific monoamine system as the primary mediator of anxiety. Lader [23] reported that the central and peripheral action of the catecholamines, mainly norepinephrine (NE), mediate arousal and emotion in general, and anxiety in particular. Reduction in serotonin (5-HT) turnover is apparently also important in the anxiolytic action of the benzodiazepines [40]. The therapeutic action of the antianxiety drugs may be due to a reduction in the activity of various ascending monoaminergic projections, i.e., noradrenergic and serotonergic to the septo-hippocampal system, noradrenergic to the hypothalamus, and dopaminergic to the frontal cortex [15].

Exploratory behavior and motor activity have been used in a number of studies as measures of emotional behavior in order to evaluate the antianxiety effects of the minor tranquilizing drugs. Consistent increases in the exploratory behavior of inexperienced (naive) mice and rats treated with chlordiazepoxide, clonazepam, or diazepam have been reported in a y-maze [27], a two-chambered, light/dark arena [6], a hole board [29], and in an open-field box [26]. Similar results have been obtained using models of anxiety involving conflict behavior [12] and aggression [25]. In a test of anxiety based on the social interaction between pairs of male rats, less change in social interaction were observed in chronic flurazepam-treated rats as the illumination and unfamiliarity of the test arena were manipulated. In other words, flurazepam prevented the reduction in social interaction that is usually evident when the test chamber is unfamiliar to the animal or is brightly lit [10].

The present study investigated the action of chlordiazepoxide (CDP) on emotional behavior of mice in an open-field box after exposure to stress. Animals were exposed to a combination of stimuli (noise, light, environmental change) which unlike cold swim, footshock, or other physical stressors, were considered psychological stressors free of debilitating effects. The relationship of the monoamines to the mediation of emotional responsiveness to stress was investigated by combining monoamine receptor

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agonist treatment (quipazine, a 5-HT agonist; apomorphine, a DA agonist; clonidine, a NE agonist) with CDP administration.

METHOD

Animals

Male mice of the CD-1 strain (Carworth Farms, Wilmington, MA), 90–150 days old, were housed five to a cage with food and water available ad lib. The laboratory was maintained at a temperature of 21°C, with a light cycle of 12 hr on, 12 hr off. All procedures were performed during the animals' active period between the second and fifth hours of the dark cycle.

Apparatus

Acute stress treatment involved a combination of three relatively mild stressors: (1) broad band noise (100–105 dB SPL) for 30 minutes generated by a Grason-Stadler noise generator, (2) close exposure to light produced by two 40 W bulbs, and (3) placement in a standard size polypropylene mouse cage (28×18×12 cm) fitted with eight metal plates, each measuring 6.5×5.5 cm. Locomotor activity was assessed in an open-field chamber which was 75.2×37.2 cm and blocked off into six squares of equal area so ambulation could be measured.

Drugs

Chlordiazepoxide hydrochloride (Roche Laboratories, Nutley, NJ), apomorphine hydrochloride (Merck Sharpe and Dohme Research Laboratories, Rahway, NJ), clonidine hydrochloride (Boehringer-Ingelheim LTD, Ridgefield, CT), and quipazine maleate (Miles Laboratories, Inc., Elkhart, IN) were dissolved in 0.9% saline. Injections were given intraperitoneally in a volume of 2.5 ml/kg body weight. Doses of CDP, apomorphine, and clonidine were calculated as hydrochloride while quipazine was calculated as maleate. Drug solutions were prepared to be used for two consecutive days, except apomorphine which was freshly prepared prior to injection. Dose levels of CDP used were 5, 10, 20 and 40 mg/kg. Agonist treatment was administered at the following doses: quipazine, 0.5 mg/kg; apomorphine, 0.5 mg/kg; and clonidine, 0.1 mg/kg. Doses were originally selected on the basis that they were to be high enough to produce receptor stimulation, while at the same time, cause minimal behavioral change when administered alone.

Procedure

The study employed two stress levels (stress and no stress), four dose levels of acute CDP treatment and a saline control, and three separate agonist treatments and a saline control in a combined 2×5×4 complete factorial design. An animal in the stress condition was injected with the appropriate dose of CDP and agonist treatment successively and placed back into its home cage. Twenty min later, the mouse was retrieved from its home cage, placed into the standardized mouse cage fitted with eight metal plates, and transported to a sound attenuated room for stress exposure. Immediately following the stress session, animals were tested in the behavioral apparatus or sacrificed for neurochemical analysis. Animals not exposed to stress were treated in an identical manner except they remained in their home cages from the time of injection to the time of testing or sacrificing. Total elapsed time from injection to testing or commencement of the biochemical determinations was 50 min. Animals undergoing behavioral testing were placed into the open-field apparatus and the number of squares crossed in a 10 min period was recorded.

Animals to be used for neurochemical assays were sacrificed quickly by cervical dislocation. Brains were then removed and split equally into two halves and weighed prior to being frozen for subsequent assays. One half was used to determine the catecholamines while the other half was used to determine 5-HT and the metabolites. Procedures for quantification of the amines and their metabolites involved the use of high pressure liquid chromatography (HPLC) with electrochemical detection. Catecholamines (NE, DA) were quantified using the procedure of Wagner *et al.* [47] with modifications. Samples were put onto the HPLC unit (Bioanalytical Systems, West Lafayette, IN) which was equipped with a Bio-Sil ODS-5S, 250×4 mm, Reverse Phase Column (Bio-Rad Laboratories, Richmond, CA). The mobile phase which consisted of 0.007 M dibasic sodium phosphate, 0.015 M citric acid, 2.5–5.0% methanol, 35–50 mg octyl sodium sulfate, pH 3.85 was filtered through a Millipore system equipped with a GS 0.22 μm filter and flowed through the system at a rate of 1 ml/min. The detector was a Bioanalytical Systems model LC-3 used with a glassy carbon electrode at a potential of 0.9 V versus a silver-silver chloride reference electrode. The method of Perry and Fuller [30] was used for measuring 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) levels. Samples were put on a separate HPLC unit equipped with a Hexyl C6 HiChrom Reversible column (Regis Chemical Company, Morton Grove, IL). The mobile phase was 0.1 M dibasic sodium phosphate, 0.05 M citric acid, 10% methanol, pH 4.80. Flow rate was 0.75 ml/min for the metabolites and 1 ml/min for 5-HT. The detector was a BAS model LC-2A used with a carbon paste electrode and run at a potential of .9 V versus a silver-silver chloride reference electrode.

A fluorometric method described by Guillemen *et al.* [16] with modifications by Givener and Rochefort [13] was employed for the determination of blood plasma CS levels.

RESULTS

Two overall multivariate analyses of variance (MANOVA) for independent observations were performed, one for the behavioral measures (n=10 per cell) and another for the neurochemical data (n=5 per cell). Since the design of the study specified a control group within each agonist condition, individual treatment means were compared to the control mean using Dunnett's test [50].

Squares Crossed

The univariate tests provided by the MANOVA analysis indicated significant effects due to stress, $F(1,360)=123.35$, $p<0.001$, CDP treatment, $F(4,360)=63.64$, $p<0.001$, agonist challenge, $F(3,360)=62.23$, $p<0.001$, stress × CDP interaction, $F(4,360)=3.13$, $p<0.015$, CDP × agonist interaction $F(12,360)=3.23$, $p<0.001$, and a stress × CDP × agonist interaction, $F(12,360)=2.55$, $p<0.003$. Figure 1 shows that for the saline condition, across all doses of the drug, stressed animals crossed more squares per minute than their nonstressed counterparts. Significant increases in squares crossed for stressed mice were recorded at the 5 and 10 mg/kg doses of CDP, $t(5,360)=3.47$, $p<0.01$, and $t(5,360)=3.45$, $p<0.01$, respectively. At the highest dose of

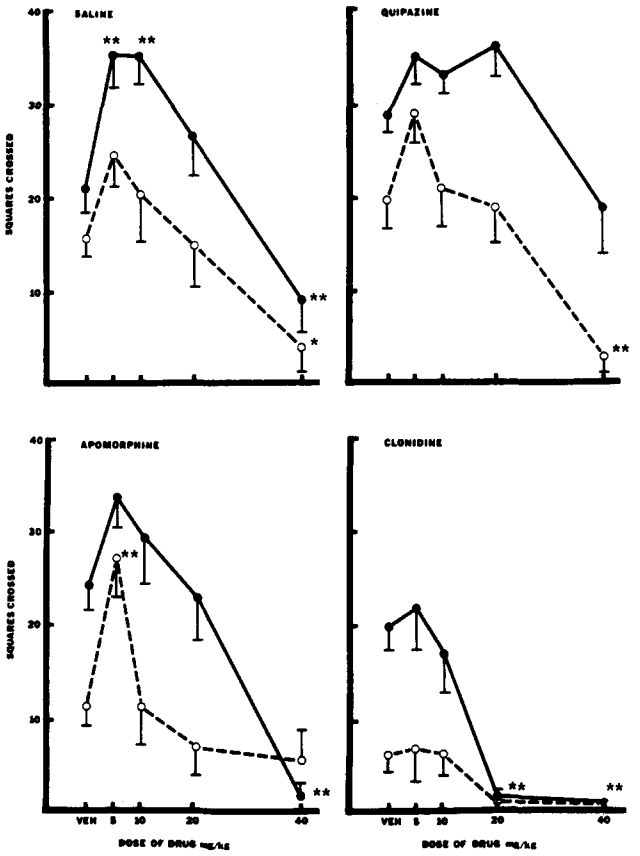

FIG. 1. Effect of chlordiazepoxide combined with agonist treatment on number of squares crossed per minute of stressed (solid circles) and nonstressed (open circles) mice. Results are given as mean with SEM (n=10). Statistical significance show differences from the VEH value for a given condition. *$p<0.05$, **$p<0.01$.

CDP, a significant decline in squares crossed was evident for the stress, $t(5,360)=3.10$, $p<0.01$, and no stress, $t(5,360)=2.93$, $p<0.05$, groups.

In comparison to saline-treated mice, quipazine, alone, markedly stimulated activity in the stressed condition, $t(4,72)=3.24$, $p<0.01$. Additional treatment with quipazine did not significantly increase ambulatory activity beyond vehicle levels, which may indicate a ceiling effect. However, the depressant effect of high doses of CDP was attenuated by quipazine. In CDP-quipazine-treated mice, locomotor activity did not decline until the highest dose of CDP was administered. Despite the drop at 40 mg/kg, the number of squares crossed for the stressed group never decreased significantly from vehicle control.

Within the apomorphine condition, the stress-no stress distinction as well as the apparent decline in response rate with the higher doses of CDP remained intact. However, at the 5 mg/kg level, nonstressed animals showed a dramatic increase in the number of squares crossed per minute compared to vehicle control, $t(5,360)=4.01$, $p<0.01$, while no significant change from vehicle was observed for the stressed group. Between 5 and 10 mg/kg of CDP for nonstressed mice, the number of squares crossed dropped sharply back to vehicle, leveling off thereafter. For the stressed group, locomotor activity decreased steadily with the three highest doses of CDP, and at 40 mg/kg was significantly below vehicle, $t(5,360)=5.84$, $p<0.01$.

The stress-no stress differences in locomotion was much greater in the group receiving only clonidine than it was in the saline-no CDP group. Clonidine treatment resulted in an attenuation of the significant increases in activity observed for saline-treated stressed animals at the 5 and 10 mg/kg doses of CDP. In addition, clonidine hastened the decrease in activity resulting from CDP administration at higher doses since at 20 and 40 mg/kg of CDP, the number of squares crossed was significantly less than vehicle control, $t(5,360)=4.71$, $p<0.01$, and $t(5,360)=4.94$, $p<0.01$, respectively.

Biochemistry

The univariate tests provided by the MANOVA analysis indicated significant effects on NE due to CDP treatment, $F(4,160)=9.84$, $p<0.001$, agonist challenge, $F(3,160)=18.97$, $p<0.001$, CDP × agonist interaction, $F(12,160)=6.34$, $p<0.001$, and a stress × CDP × agonist interaction, $F(12,160)=1.93$, $p<0.034$. Table 1 shows that when averaging across levels of stress, NE was significantly above vehicle in the clonidine groups administered stimulatory doses of CDP. This effect was opposite to that found in saline mice receiving low doses of CDP. In the latter case, NE remained at vehicle level at 5 mg/kg and was significantly depressed at 10 mg/kg of CDP.

Significant effects were obtained on 5-HIAA due to CDP treatment, $F(4,160)=9.21$, $p<0.001$, agonist challenge, $F(3,160)=6.11$, $p<0.001$, stress × CDP interaction, $F(4,160)=2.68$, $p<0.034$, stress × agonist interaction, $F(3,160)=2.72$, $p<0.047$, CDP × agonist interaction, $F(12,160)=6.67$, $p<0.001$, and a stress × CDP × agonist interaction, $F(12,160)=2.01$, $p<0.027$. For the saline condition, 5-HIAA values were above vehicle at all levels of CDP and were significantly different at the 5 and 20 mg/kg doses, $t(5,160)=2.96$, $p<0.05$, and $t(5,160)=5.00$, $p<0.01$, respectively, as reported in Table 1. Analysis for quipazine administration revealed a general dose-dependent increase in 5-HIAA. Levels of 5-HIAA peaked significantly above vehicle at 20 mg/kg, $t(5,160)=5.89$, $p<0.01$, and declined slightly at 40 mg/kg while still above the vehicle control value.

Univariate tests indicated significant effects on 5-HT due to CDP treatment, $F(4,160)=28.12$, $p<0.001$, agonist challenge, $F(3,160)=24.79$, $p<0.001$, and a CDP × agonist interaction, $F(12,160)=4.66$, $p<0.001$. Table 1 indicates that quipazine-treated animals showed significant increases in 5-HT at both 5 and 10 mg/kg of CDP, $t(5,160)=2.95$, $p<0.05$, and $t(5,160)=4.56$, $p<0.01$, respectively. Following a decline at the 20 mg/kg dose, 5-HT levels recovered and reached peak values at 40 mg/kg.

Significant effects were obtained for DA due to CDP treatment, $F(4,160)=18.07$, $p<0.001$, agonist challenge, $F(3,160)=25.03$, $p<0.001$ and the CDP × agonist interaction, $F(12,160)=8.64$, $p<0.001$. As demonstrated in Table 1, dopamine decreased to its lowest level, for all CDP-agonist combinations, with the 10 mg/kg CDP-saline group. Thereafter, as the dose of CDP increased, DA levels rose and were significantly greater than vehicle at 40 mg/kg, $t(5,160)=3.48$, $p<0.01$. In the apomorphine-treated group, DA levels dropped significantly below vehicle at 5 mg/kg of CDP. However, in contrast to saline treatment, DA levels rebounded and were significantly greater than vehicle control

TABLE 1

EFFECT OF CHLORDIAZEPOXIDE AND AGONIST DRUG TREATMENT ON WHOLE BRAIN LEVELS OF THE MONOAMINES AND THEIR METABOLITES

Treatment	NE	DA	5-HT	5-HIAA
Saline + Saline	0.47 ± 0.01	1.29 ± 0.04	0.53 ± 0.01	0.36 ± 0.01
+ 5 mg/kg CDP	0.47 ± 0.01	1.21 ± 0.03	0.50 ± 0.01	0.41 ± 0.01*
+ 10 mg/kg CDP	0.41 ± 0.02*	1.09 ± 0.03†	0.56 ± 0.01	0.38 ± 0.01
+ 20 mg/kg CDP	0.46 ± 0.01	1.34 ± 0.02	0.59 ± 0.02	0.45 ± 0.02†
+ 40 mg/kg CDP	0.49 ± 0.01	1.47 ± 0.05†	0.63 ± 0.03†	0.39 ± 0.02
Quipazine + Saline	0.46 ± 0.02	1.24 ± 0.04	0.50 ± 0.01	0.37 ± 0.01
+ 5 mg/kg CDP	0.45 ± 0.01	1.21 ± 0.03	0.57 ± 0.02*	0.39 ± 0.01
+ 10 mg/kg CDP	0.47 ± 0.01	1.34 ± 0.03	0.61 ± 0.01†	0.45 ± 0.02†
+ 20 mg/kg CDP	0.43 ± 0.01	1.17 ± 0.02	0.55 ± 0.01	0.46 ± 0.01†
+ 40 mg/kg CDP	0.51 ± 0.02*	1.44 ± 0.02†	0.70 ± 0.02†	0.42 ± 0.01†
Apomorphine + Saline	0.53 ± 0.02‡	1.44 ± 0.04‡	0.57 ± 0.02	0.42 ± 0.01‡
+ 5 mg/kg CDP	0.46 ± 0.02†	1.30 ± 0.04*	0.51 ± 0.02*	0.41 ± 0.01
+ 10 mg/kg CDP	0.49 ± 0.01	1.57 ± 0.04*	0.59 ± 0.01	0.38 ± 0.01*
+ 20 mg/kg CDP	0.51 ± 0.02	1.37 ± 0.03	0.54 ± 0.02	0.43 ± 0.01
+ 40 mg/kg CDP	0.55 ± 0.01	1.56 ± 0.05	0.60 ± 0.02	0.37 ± 0.01*
Clonidine + Saline	0.43 ± 0.01	1.10 ± 0.03‡	0.62 ± 0.03‡	0.38 ± 0.01
+ 5 mg/kg CDP	0.48 ± 0.02*	1.33 ± 0.03†	0.59 ± 0.02	0.35 ± 0.01
+ 10 mg/kg CDP	0.54 ± 0.01†	1.30 ± 0.04†	0.61 ± 0.01	0.42 ± 0.01
+ 20 mg/kg CDP	0.54 ± 0.02†	1.40 ± 0.03†	0.70 ± 0.01*	0.38 ± 0.01
+ 40 mg/kg CDP	0.54 ± 0.02†	1.36 ± 0.06†	0.70 ± 0.02†	0.41 ± 0.01

Results are given as mean (μg/g) with ±SEM (n=10). Statistical significance show differences from the drug + saline value for a given agonist drug treatment condition, *$p<0.05$, †$p<0.01$. Statistical significance between agonist + saline and saline + saline, ‡$p<0.05$.

at 10 mg/kg of CDP, $t(5,160)=2.59$, $p<0.05$. As was the case with NE, the change in DA levels at low doses of CDP with clonidine was opposite to that observed for saline-treated mice. In clonidine-treated animals, DA was significantly above vehicle at 5 and 10 mg/kg of CDP whereas for saline-treated mice, DA declined at 5 mg/kg and was significantly below vehicle at 10 mg/kg of CDP. Exposure to stress produced an approximate two-fold increase in plasma corticosterone levels. Basal CS levels were 13.9±1.6 μg/100 ml plasma. With the addition of the stressful stimuli, CS levels increased three-fold to 38.3±2.4 μg/100 ml, $t(18)=8.46$, $p<0.001$.

DISCUSSION

Depending upon dosage of administration, acute CDP treatment appeared to produce two distinct and opposing pharmacological actions on behavior. In non-stressed animals, locomotor activity displayed after acute treatment with CDP followed an inverted U-shaped curve. This result is consistent with earlier findings indicating that low doses of diazepam (0.5 mg/kg) increased activity of male albino mice whereas doses greater than 2.0 mg/kg caused a considerable dose-related decrease [45]. Acute treatment with 5 and 10 mg/kg of CDP led to increases in spontaneous locomotor activity of mice in the early stages of a 60 min activity test whereas higher doses (20 and 30 mg/kg) had significant depressant effects [34]. Similar effects on locomotor activity of acute CDP injection have been confirmed by other investigators [5, 18, 19, 22].

Rather than producing an "emotional" animal exhibiting reduced ambulatory activity [3, 7, 33, 48], exposure to acute stress in the present study led to behavioral activation. Without drug pretreatment, stressed animals crossed more squares than their nonstressed counterparts. This finding is consistent with the results of Katz *et al.* [20] who reported an activation response in rats given one hour of 95 dB white noise in a brightly lit room (8×70 W lamps). According to the dose-response curves of the present study, the facilitatory effects of CDP is sustained for a longer period in animals subjected to noise stress. In stressed as compared to nonstressed mice, more drug is needed to show a comparable decrease in locomotor activity.

Consistent increases in 5-HIAA were observed suggesting that turnover of 5-HT was increased by CDP. In stressed and nonstressed mice, combined CDP/quipazine also resulted in increases in 5-HIAA. In addition, at doses of 5, 10 and 40 mg/kg of CDP, quipazine produced significant increases in endogenous levels of 5-HT. Although the changes in 5-HIAA and 5-HT may not directly reflect the 5-HT receptor stimulatory effect of quipazine, they may yet be indicative of increase serotonergic activation. The behavioral and neurochemical changes resulting from quipazine treatment indicate that the proposed anti-serotonergic action of CDP is not responsible for the stimulatory effect of the drug. Sansone [36] reported that CDP and two 5-HT receptor antagonists exerted opposite effects on behavior in morphine-treated mice. Chlordiazepoxide enhanced morphine-induced hyperactivity whereas cyproheptadine and mianserin antagonized the locomotor stimulation. Others have not supported

a reduction in 5-HT turnover as the mechanism of action of the benzodiazepines [39].

Numerous studies have established the fact that 5-HT and its precursors, and directly acting serotonergic agonists, inhibit drug-induced and spontaneous locomotor activity [14, 21, 24, 49]. The finding that quipazine, an alleged 5-HT agonist, did not block locomotor activity suggests the possibility that quipazine exerted its effects through the involvement of other system besides 5-HT. A dopaminergic component to the action of quipazine has been proposed [9]. Quipazine injected bilaterally into the nucleus accumbens septi increased locomotor activity in rats. Injections of methysergide, a 5-HT antagonist, failed to inhibit this locomotor activity whereas haloperidol, a DA blocking agent, antagonized the locomotor hyperactivity induced by quipazine.

The involvement of catecholaminergic mechanisms in the stimulatory action of CDP on locomotor and exploratory activity has been suggested [46]. Increased catecholaminergic activity may be responsible for the enhancement of amphetamine-induced locomotor stimulation by CDP [35], as well as the strong stimulatory effects exerted by CDP-morphine combinations [38].

The finding that clonidine inhibited locomotor activity may be taken to indicate that the stimulatory effect of CDP is due to enhanced catecholaminergic neurotransmission. Clonidine pretreatment in stressed mice prevented the increase in ambulatory activity seen with low doses of CDP and hastened the depressant effects of the drug. Drew *et al.* [8] reported that intraperitoneal injection of clonidine (0.05–0.2 mg/kg) caused dose-dependent sedation in rats. Drew *et al.* [8], along with other investigators who have reported similar effects with single small doses of clonidine [32, 41, 51], have attributed these effects to stimulation of presynaptic α_2-adrenoceptors. The consequence of presynaptic receptor stimulation is a reduction in NE activity which may be a reflection of decreased utilization of NE and an inhibition of firing of NE neurons [1, 2, 44].

The neurochemical results of the present experiment favor a possible reduction of NE activity as the mechanism of action of clonidine. Clonidine, by activating presynaptic NE receptors, may be inhibiting NE transmission and antagonizing the catecholamine-enhancing effect of stimulatory doses of CDP. As a consequence, NE levels are increased and behavior is depressed. Along with its effects on NE activity, clonidine has been shown to affect the DA system. Clonidine was reported to inhibit DA neurotransmission and decrease gross locomotor activity in mice [42]. In the present study, DA levels were significantly elevated after clonidine administration.

Apomorphine administered in low doses has been shown to decrease locomotor activity in rats and mice due, probably, to inhibition of DA neurotransmission via stimulation of presynaptic DA autoreceptors [37, 38, 43]. Averaging across stress levels, apomorphine did not appear to antagonize the increase in locomotor activity observed at the 5 mg/kg dose of CDP. As the dose of CDP increased and the effect of the drug changed, the antagonistic effect of apomorphine became more evident. With the high doses of CDP possibly acting to depress catecholamine activity (NE and DA), apomorphine's action became additive. The direction of change in DA from no CDP to 5 mg/kg was similar in both saline- and apomorphine-treated mice which may account for the absence of an antagonistic effect of apomorphine on behavior. However, at the 10 mg/kg dose of CDP in the saline condition, DA levels declined further and were significantly below vehicle whereas, in the apomorphine group, the opposite occurred and DA increased significantly above vehicle. This difference, neurochemically, may reflect the appearance of the inhibitory effect of apomorphine on behavior as the dose of CDP increased and its depressant effects on locomotor activity were developing. When combined across levels of stress, locomotor activity in the saline group was still significantly above vehicle whereas, in the apomorphine group, activity exhibited a steeper decline from 5 to 10 mg/kg of CDP.

In summary, the interaction of CDP pretreatment and monoamine receptor agonist drugs was investigated to determine the relative roles of central NE, DA and 5-HT in the action of CDP. Behavioral and biochemical findings are consistent with a role for the catecholamines in the locomotor stimulatory effects of CDP.

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