Pharmacology Biochemistry and Behavior, Vol. 66, No. 2, pp. 403–411, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(00)00178-7

Behavioral Effects Of 8-OH-DPAT in Chronically Stressed Male and Female Rats

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Received 12 February 1999; Revised 20 October 1999; Accepted 17 November 1999

SIPOS, M. L., R. A. BAUMAN, J. J. WIDHOLM AND G. J. KANT. *Behavioral effects of 8-OH-DPAT in chronically stressed male and female rats.* PHARMACOL BIOCHEM BEHAV **66**(2) 403–411, 2000.—The present study tested the hypothesis that chronic stress desensitizes serotonergic 5-HT_{1A} receptors and alters behavioral changes following 5-HT_{1A} agonist administration. Eating, acoustic startle response (ASR), and locomotor activity were measured in stressed and nonstressed male and female rats after 8-OH-DPAT administration. Stressed rats were paired and stressed by around-the-clock intermittent foot shock. Controllable stress (CS) rats could avoid/terminate shock for themselves and their yoked partners by pulling a ceiling chain, whereas their partners, the uncontrollable stress (UCS) rats, could not. Rats earned their entire daily ration of food by pressing a lever. In previous experiments, this paradigm was stressful, but not debilitating and rats continued to eat, groom, sleep, and avoid/escape greater than 99% of shock trials. Locomotor activity and ASR were measured in the present study after saline and 8-OH-DPAT administration (0.25 mg/kg, IP) before, 24 h, and 72 h after shock onset. 8-OH-DPAT only decreased food intake significantly in male and female rats after the first administration. Stress decreased food intake in both the CS and UCS rats, with UCS rats eating the least. However, the effects of stress and 8-OH-DPAT were not additive. 8-OH-DPAT significantly increased peak startle amplitude at 100 and 120 dB, and decreased latency to peak startle amplitude at 100 dB in male and female rats. In contrast, 8-OH-DPAT did not alter percent prepulse inhibition (%PPI) at 100 dB, but significantly decreased %PPI in males but not females at 120 dB. Stress did not have a consistent effect on ASR, but reduced %PPI in males, but not females. Neither stress nor 8-OH-DPAT significantly altered locomotor activity. Although the results do not show an increased sensitivity to 8-OH-DPAT in stressed rats, the unexpectedly weak effects of 8-OH-DPAT alone on the behavioral measures chosen limits the conclusions that can be drawn. © 2000 Elsevier Science Inc.

Serotonin Chronic stress Locomotor activity Figure-8 maze Acoustic startle response 8-OH-DPAT 5-HT_{1A} receptors

STRESS is thought to contribute to physical and mental illness in civilians and be the major source of psychiatric casualties in combat (3,6,16,27,31,43–45,60,70). Improved therapeutics designed to treat stress-related illnesses are clearly needed. Yet, controlled scientific studies of sustained stress in humans are technically and ethically difficult. Even in laboratory animals, however, the vast majority of stress research has been conducted using stress of short duration.

Uncontrollable stress, in general, has been reported to cause profound physiological and behavioral disruptions as assessed by a variety of end points. Our laboratory has conducted a long-term effort to characterize the effects of sustained stress on physiology and behavior using a stress paradigm in male and female rats modeling the sustained stress soldiers might experience during sustained operations (4,5,9, 10,35–37,39). For example, we have found sustained stress altered stress-responsive hormone levels (35,38), feeding (36), body weight (4), thymus weight (unpublished data), biological rhythms (36), sleep patterning (39), and acquisition and performance in fixed-interval and delayed alternation tasks (10,37). Stress can have similar effects in humans, and has been reported to alter food intake, plasma cortisol levels, immune function, biological rhythms, and impair learning and/or memory (3,60,70).

Most of the changes in physiology following sustained stress are less pronounced in animals that can avoid or terminate stressors compared to animals that have no control over stressor duration (35,72,73). Consequently, our sustained stress paradigm included control rats that received no shock, as well as two groups of stressed rats. One group of stressed rats had control over stressor termination, while the other group did not. Although this paradigm was stressful, it was

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not debilitating, and rats continued to eat, sleep, groom, avoid, or escape greater than 99% of presented shock trials, and gradually regained body weight lost during the first days of stress exposure.

Stress also appears to alter normal serotonergic neurotransmission. For example, serotonin turnover is increased following acute stress (29,32,57,63). Although less is known about the long-term alterations in serotonergic neurotransmission caused by sustained stress, the efficacy of serotonin selective reuptake inhibitors in treating depression suggests that serotonin may be involved in the development or expression of stress-related depression. Sustained stress has been reported to desensitize 5-HT_{1A} receptors in rodents, possibly due to increased release of serotonin or through stress-induced increases in corticosterone (14,19,49,50,52,56,69,71).

The present study was conducted to determine if sustained stress could alter the behavioral responses expected following the administration of 8-OH-DPAT, a 5-HT_{1A} agonist. Treatment with 8-OH-DPAT has been found to increase food intake (11,12,23,25,33,62), increase peak startle amplitude (55,67,77), decrease prepulse inhibition (58,64), and have mixed effects on locomotor activity (2,18,26,30,75). As such, we hypothesized that sustained stress would desensitize the serotonergic system and reduce the behavioral changes expected following 8-OH-DPAT administration in stressed rats compared to unstressed controls.

METHOD

Animals

Male (n = 18) and female (n = 18) Sprague–Dawley rats were purchased from Charles River Laboratories (Raleigh, NC), quarantined, and checked for health status in the Walter Reed Army Institute of Research Quarantine Facility. Rats were housed individually in hanging cages with food and water available ad lib, and were maintained on a 12 L:12 D cycle (lights on at 0800 h). Male rats weighed between 305 and 445 g (mean: 383 g) at the beginning of the experiment, whereas female rats weighted between 216 and 326 g (mean: 259 g) at the beginning of the experiment.

General Procedures

In each of the three experiments, six male and six female rats were divided equally among the nonstressed rats (n = 2), controllable stress rats (n = 2), and uncontrollable stress rats (n = 2). In each experiment, the rats were brought to the experimental environmental chamber, weighed, and placed in individual operant cages housed inside sound-attenuating chambers (Coulbourn Instruments, Allentown, PA). The houselights in the boxes were illuminated from 0800 to 2000 h daily, food pellets were available by pressing a lever (FR 1), and water was freely available. Rats were allowed to habituate to the chambers and were trained to press a lever for food (45-mg pellets, Noyes Formula A, 60% carbohydrate (5% sucrose), 24% protein, 4% fat; P. J. Noyes, Lancaster, NH).

In all three experiments, the following experimental timeline was followed using the onset of the shock trials as day 0 (see Table 1). The rats were familiarized with the Figure-8 maze and the acoustic startle chambers 1 week prior to the onset of the shock trials. The rats were tested for activity and acoustic startle response (ASR) following saline administration during two trials that were separated by 90 min on day −5. The rats were tested for activity and ASR on day −1, first following saline administration and again 90 min later following 8-OH-DPAT administration. The controllable stress rats were trained to "control stress" by pulling a ring attached to a ceiling chain to avoid or escape shock on the morning of day 0. Both the controllable stress and uncontrollable stress groups were exposed to around-the-clock intermittent footshock (approximately one trial/5 min) until the experiment ended 72 h later on day +3. The rats were tested for activity and acoustic startle again on day +1 (24 h after shock onset) and day +3 (72 h after shock onset) using the same injection schedule as described above.

Chronic Stress

Rats assigned to the controllable stress (CS) group were trained to pull a ring attached to a ceiling chain to escape shock. Each CS rat was yoked to a rat assigned to the uncontrollable stress (UCS) group such that the UCS rat received shock simultaneously with the CS rat being trained to escape shock. After each CS rat was trained, a procedure that generally required no more than 30 min of intermittent shock, shock delivery was controlled by a PDP11 computer programmed in SKED (66). Shock presentation trials began with a 5-s illumination of a triple cue lamp, followed sequentially by a 5-s sonalert auditory warning tone, and then 5 s each of 0.16, 0.32, 0.65, 1.3, and finally 2.6 mA of foot shock. Shock delivery could be avoided or escaped at any point in the trial sequence by the CS rat pulling the ceiling chain. The UCS rats had no control over shock delivery; shock was turned off for both the UCS and CS rat whenever the CS rat pulled the chain. For the first 35 trials, shock trials were initiated at average intertrial intervals of 1 min. Following 35 successful escapes, the average intertrial interval was increased to 5 min.

TABLE 1
EXPERIMENTAL TIME LINE

Day	Shock*	Inject 1	Startle 1	Activity 1	Inject 2	Startle 2	Activity 2
−5	No	Saline	Yes	Yes	Saline	Yes	Yes
−2 to −4	No	None	No	No	None	No	No
−1	No	Saline	Yes	Yes	DPAT	Yes	Yes
0	Yes	None	No	No	None	No	No
+1	Yes	Saline	Yes	Yes	DPAT	Yes	Yes
+2	Yes	None	No	No	None	No	No
+3	Yes	Saline	Yes	Yes	DPAT	Yes	Yes

*No shock ever in nonstressed control group. On day 0, rats were trained to avoid/escape shock and then around-the-clock intermittent footshock commenced. Drug injections and startle/activity testing were conducted on a staggered schedule beginning with the first saline injection to the first rat at approximately 1300 h and ending with the final activity test to the 12th rat at approximately 1630 h. All drug injections were administered between 1430 and 1530 h.

Shock trials were terminated if 20 consecutive escape failures were recorded, but this condition was never met. The number of lever presses and avoidance/escape chain pulls were recorded, and individual chain pulls were tagged with an identifier to indicate whether the pull occurred during the light, tone, or one of the five shock levels. In previous experiments, we found that the CS rats avoid or escape more than 99% of the approximately 280 trials presented each day.

Drugs

(±)-8-Hydroxy-dipropylaminotetralin HBr [(±)-8-OH-DPAT] was purchased from Research Biochemicals International (Natick, MA). The drug was dissolved in 0.9% saline, and prepared fresh every day. Rats were administered 0.25 mg/kg (expressed as the salt) in a volume of 1 ml/kg intraperitoneally. This dose was selected based on doses that we expected to produce both super- and subsensitive responses (7,12,30,62). Peak plasma and brain concentrations of 8-OH-DPAT are reached quickly (5–15 min), but behavioral effects can be seen for longer periods (59,76). All drug injections were administered between 1430 and 1530 h, but to avoid any possibility of drug carryover, repeated injections were separated by 48 h.

Food Intake

The number of lever presses for food were recorded 24 h/day. Twenty-four-hour food totals and data collected between 1600 and 2200 h were used to assess the effects of stress on food intake. The 6-h data collection period included both light (4 h) and dark (2 h) periods and occurred after 8-OH-DPAT administration and immediately following both ASR and locomotor activity testing. Only the 6-h data were used to assess the effects of 8-OH-DPAT administration on food intake.

Acoustic Startle Response Testing

Acoustic startle response amplitudes, latencies, and percent prepulse inhibition were tested simultaneously in a SR-Lab Startle Response System (San Diego Instruments, San Diego, CA), which consisted of a computer control unit and four startle chambers. Each startle chamber consisted of a Plexiglas cylinder (8.2 cm in diameter and 20.5 cm in length) resting on a Plexiglas base placed in a ventilated, sound-attenuated chamber. Movements within the cylinder were detected and transduced by a piezoelectric accelerometer attached to the Plexiglas base. The platforms were calibrated for accuracy daily and were adjusted to 150 ± 3 units using a standard calibrator tube (San Diego Instruments).

Fifteen minutes after vehicle or drug administration, each rat was placed in a Plexiglas cylinder and the sound-attenuating chamber was closed. Each test session was preceded by a 3-min chamber adaptation period, during which the background noise level was set to 60 dB. Acoustic startle pulses consisting of 0, 70, 100, or 120-dB white noise bursts, sometimes preceded by 70-dB prepulses, were presented through a loudspeaker mounted 24 cm above the animal. The sound levels were verified using a Realistic (RadioShack) sound level meter with the microphone placed in the position of the subject's head. There were 10 of each of six types of stimulus trials, presented in a randomized block design. The trial types consisted of 100-dB noise bursts alone or with prepulses, 120-dB noise bursts alone or with prepulses, prepulse-alone trials, and no stimulus trials for a total session consisting of 60 trials. Interstimulus intervals ranged randomly between 10 and 20 s.

Following each stimulus presentation, an animal's movement was measured for a period of 200 ms by the computer control unit that controlled stimulus presentation and data collection. Peak startle amplitude (VMAX) was recorded as the highest voltage occurring during the 200 ms window following stimulus presentation. Latency to VMAX (TMAX) was recorded as the time in ms after stimulus presentation at which the peak startle amplitude occurred. Finally, percent prepulse inhibition (%PPI) measures were calculated as the difference between the pulse-alone and the prepulse + pulse trials, divided by the pulse alone, multiplied by 100. Percent scores are typically used to minimize the effect of individual variation of startle amplitude on PPI (47). Thus, a high %PPI score indicates that the prepulse inhibited the response to the startling stimulus, whereas a low %PPI score indicates a disruption in the sensorimotor gating mechanism (28).

Locomotor Activity

Locomotor activity was measured using a "Figure-8" Photobeam Activity System (San Diego Instruments). The Plexiglas enclosure contained eight separately counted infrared photobeams. Activity was measured after ASR measurements for 10 min in dim light 40 to 55 min after drug injection. The total number of beam breaks occurring during the 10-min trial was analyzed.

Data Analyses

Locomotor activity and food intake were analyzed by analysis of variance (ANOVA), with selected post hoc comparisons performed using the Student's *t*-test following a significant overall *F*-score. Acoustic startle responses were analyzed using a 1-within, 1-between repeated-measures ANOVA to examine gender and drug treatment interactions, and a 2-within, 1-between, repeated-measures ANOVA to examine drug treatment, gender, and stressor interactions. Results were considered to be significant at $p < 0.05$.

RESULTS

Effects of Gender, 8-OH-DPAT, and Stress on Food Intake

Prior to stress exposure, male rats lever pressed significantly more than females for food per day [600 ± 32 vs. 373 ± 25 presses; $F(1, 334) = 93$, $p < 0.0001$]. Overall, females earned 38% fewer pellets than males, but females also weighed 32% less than males. Following stress onset, daily food intake in the controllable stress (CS) and uncontrollable stress (UCS) groups was decreased compared to same-sex rats in the nonstressed group (see Table 2). Stress significantly reduced the total number of lever presses for food per day in both males, $F(2, 60) = 18.8$, $p < 0.001$, and females, $F(2, 60) = 10.2$, $p < 0.001$. Stress also significantly decreased the total number of lever presses for food during the 6 h following behavioral testing in both males [see Table 3, $F(2, 90) = 9.51$, $p < 0.001$] and females, $F(2, 90) = 5.46$, $p < 0.01$. For both males and females, rats in the CS and UCS groups lever pressed less than the nonstressed rats for each of the 4 stress days (day 0, +1, +2, and +3), and UCS rats lever pressed less than CS rats. However, these differences were only statistically significant on the first day of stress (day 0).

The effects of 8-OH-DPAT on food intake were assessed using data from the 6-h time interval. The total food intake for day −5 to day +3 are presented in Table 3. The males in the nonstressed group lever pressed 223 ± 19 times for food, and the females in the nonstressed group lever pressed 139 ±

TABLE 2
EFFECTS OF STRESS AND 8-OH-DPAT ON 24-H FOOD INTAKE

Stress Drug	Stress (Day 0) None	Stress (Day +1) DPAT	Stress (Day +2) None	Stress (Day +3) DPAT
Males				
Nonstressed	672 ± 52	561 ± 53	664 ± 29	572 ± 34
Controllable stress	393 ± 86*	450 ± 62	500 ± 67*	520 ± 37
Uncontrollable stress	250 ± 60*	330 ± 78*	462 ± 41*	462 ± 43*
Females				
Nonstressed	462 ± 33	379 ± 33	450 ± 37	378 ± 26
Controllable stress	416 ± 28	317 ± 26	378 ± 41	330 ± 24
Uncontrollable stress	297 ± 42*	283 ± 54	302 ± 63*	284 ± 53

Mean 24-h food intakes ± SEM for $n = 6$ per group.
*Significantly different from same-sex nonstressed group on same day. Stress exposure began on day "0" for controllable and uncontrollable stress groups.

19 times for food (37% of the 24-h totals for each gender) between 1600 and 2200 h on the vehicle–vehicle treatment day (day −5). Two-way (stress × day) analyses of variance were performed for the 6-h food intake totals for both males and females. The interaction between stress and day was not significant for males, $F(10, 90) = 1.60$, p = NS, or females, $F(10, 90) = 0.97$, p = NS. However, there was a significant effect of stress and day for males, $F(2, 90) = 9.51$, $p < 0.001$, and, $F(5, 90) = 3.7$, $p < 0.01$, respectively, or females, $F(2, 90) = 5.5$, $p < 0.01$, and $F(5, 90) = 3.0$, $p < 0.05$, respectively. Post hoc comparisons were conducted, and compared each 8-OH-DPAT treatment day with either the previous vehicle or no-drug day. Treatment with 8-OH-DPAT decreased food intake in both males and female rats after its first administration on the day prior to stress onset (see Table 3). Nonstressed males, CS males, CS females, and UCS females pressed significantly less for food following treatment with 8-OH-DPAT than following vehicle injection. Subsequent 8-OH-DPAT treatments in nonstressed males and females on either day +1 or day +3 decreased food intake compared to food intake on the no-drug day, but the decrease was not significant. Similarly, there were no significant differences in food intake in males or females for the CS and UCS groups following 8-OH-DPAT compared to food intake on the no-drug day.

Thus, it appears that baseline food intake in male and female rats was proportional to body weight. 8-OH-DPAT treatment only decreased food intake significantly following the first administration in both male and female rats, but did not significantly affect food intake on subsequent administrations. Stress decreased food intake in both male and female rats with the larger decreases seen in the UCS group. And finally, 8-OH-DPAT administration did not potentiate stress-induced decreases in lever pressing for food.

Effects of Gender, Stress, and 8-OH-DPAT on Acoustic Startle Responses

Two ASR test sessions were administered 90 min apart on each test day. As such, we examined whether repeated ASR sessions alone affected VMAX, TMAX, and %PPI following vehicle injections (day −5). No significant interaction existed between sessions and gender for VMAX, TMAX, or %PPI measures at 100 or 120 dB. Similarly, there was no main effect of sessions on VMAX, TMAX, or %PPI at 100 or 120 dB. Finally, only two significant main effects of gender were seen (data not shown). First, females showed significantly higher VMAX scores than males at 100 dB, $F(1, 42) = 5.59$, $p < 0.03$. Second, females showed significantly less %PPI than males at 120 dB, $F(1, 42) = 4.15$, $p < 0.05$.

The effects of 8-OH-DPAT administration (day −1) on VMAX, TMAX, and %PPI are presented in Fig. 1. There were no significant interactions between gender and drug

TABLE 3
EFFECTS OF STRESS AND 8-OH-DPAT ON 6-H FOOD INTAKE

Stress Drug	Prestress (Day −5) Vehicle	Prestress (Day −1) DPAT	Stress (Day 0) None	Stress (Day +1) DPAT	Stress (Day +2) None	Stress (Day +3) DPAT
Males						
Nonstressed	223 ± 19	126 ± 35*	243 ± 30	215 ± 42	259 ± 24	202 ± 22
Controllable stress	214 ± 26	126 ± 35*	117 ± 45†	151 ± 42	170 ± 35	198 ± 34
Uncontrollable stress	167 ± 20	129 ± 32	34 ± 16	96 ± 40	202 ± 30	155 ± 30
Females						
Nonstressed	139 ± 22	108 ± 27	184 ± 16	138 ± 20	160 ± 21	134 ± 16
Controllable stress	154 ± 28	68 ± 19*	128 ± 17†	134 ± 20	140 ± 17	132 ± 12
Uncontrollable stress	148 ± 21	83 ± 26*	93 ± 21†	107 ± 18	93 ± 19	106 ± 21

Mean 6-h food intakes ± SEM for n = 6 per group.
*Significantly different from prestress vehicle day in same treatment group.
†Significantly different from nonstressed group on same day. Stress exposure began on day "0" for the controllable and uncontrollable stress groups.

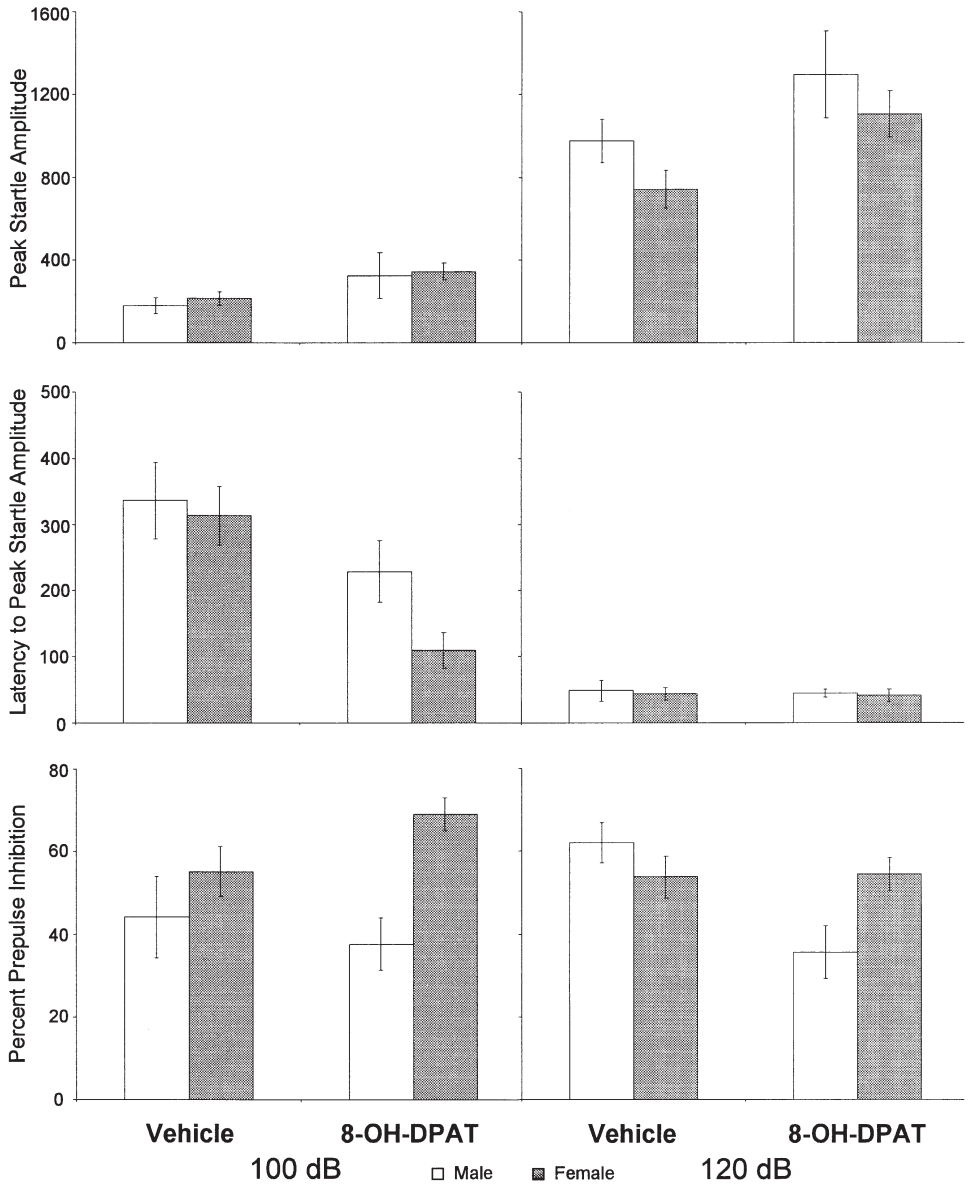

FIG. 1. Mean (±SEM) peak startle amplitudes (top), latency to peak startle amplitude (middle), and percent prepulse inhibition (bottom) in male and female rats given either vehicle or 8-OH-DPAT for 100 dB (left column) or 120 dB (right column) pulses.

treatment for VMAX and TMAX at 100 or 120 dB. However, there was a significant interaction between gender and drug treatment for %PPI at 120 dB, $F(1, 46) = 9.83, p < 0.004$, but not at 100 dB. At 120 dB, %PPI was significantly reduced in males following 8-OH-DPAT treatment, but did not change in females. Furthermore, treatment with 8-OH-DPAT significantly increased VMAX in both males and females at 100 dB, $F(1, 46) = 6.69, p < 0.02$, and 120 dB, $F(1, 46) = 11.33, p < 0.002$. Similarly, 8-OH-DPAT significantly reduced TMAX values at 100 dB in both males and females, $F(1, 46) = 17.89, p < 0.0002$, but not at 120 dB, possibly due to a floor effect.

In general, stress did not reliably affect ASR in male or female rats at 100 or 120 dB for any ASR measure following vehicle injection. For example, there was a significant effect of stress on VMAX at 120 dB after 24 h of stress, $F(2, 42) = 5.27, p < 0.01$, but not following 72 h of stress, $F(2, 30) = 2.07$, $p =$ NS. Stress did not significantly affect VMAX after 24 h or 72 h of stress at 100 dB, and did not significantly affect TMAX at either sound intensity at either time point. It was interesting to find, however, that a significant interaction between stress type and gender existed when looking at %PPI at 100 dB (see Table 4). Stress significantly reduced %PPI in males, but not in females, $F(2, 42) = 3.65, p < 0.04$, following 24 h of stress. This interaction was not significant following 72 h of stress, but the pattern of results was similar and just missed significance, $F(2, 30) = 3.048, p = 0.062$. Similarly, the interaction between stress and gender was not significant at 120 dB following 24 h of stress, $F(2, 42) = 1.33, p =$ NS. However,

TABLE 4
INTERACTION BETWEEN STRESS AND GENDER ON PERCENT PREPULSE INHIBITION FOLLOWING 24-H (DAY +1) AND 72 H (DAY +3) STRESS

Stress Decibels	Stress (Day +1) 100 dB	Stress (Day +3) 100 dB	Stress (Day +1) 120 dB	Stress (Day +3) 120 dB
Males				
Nonstressed	61 ± 5.4*	61.2 ± 8.9	61.1 ± 7.7	68.5 ± 6.0*
Controllable stress	17.5 ± 6.0*	−17.6 ± 20.7	43.4 ± 12.1	42.6 ± 15.4*
Uncontrollable stress	39.7 ± 13.8*	−15.1 ± 23.3	21.6 ± 20.1	34.1 ± 17.3*
Females				
Nonstressed	59.4 ± 10.6	44.4 ± 22.8	67.3 ± 5.6	44.4 ± 8.5
Controllable stress	63.2 ± 8.4	47.2 ± 14.3	63 ± 5.3	63.9 ± 4.5
Uncontrollable stress	56.4 ± 5.3	43.6 ± 16.1	63.1 ± 6.8	67.5 ± 4.7

Percent prepulse inhibition ± SEM for $n = 6$ per group.
*Stress significantly reduced percent prepulse inhibition in males but not in females on same day.

the pattern of results was similar to that seen at 100 dB. Following 72 h of stress, the interaction between stress and gender was significant when looking at %PPI at 120 dB, with stress significantly reducing %PPI in males, but not females, $F(2, 30) = 4.02$, $p < 0.03$. Finally, there was no significant interaction between stress, gender, and 8-OH-DPAT administration on any of the ASR measures taken following either 24 or 72 h or stress at either 100 or 120 dB.

Effects of Gender, Stress, and 8-OH-DPAT, on Locomotor Activity

Two activity trials were performed 90 min apart on each test day. As such, we examined whether repeated trials alone affected locomotor activity in the Figure-8 maze. As expected, the rats were significantly less active during the second trial than during the first trial of the day, $F(1, 68) = 13.8$, $p < 0.001$. As a result of the significant trial order effect, only the data from the second trial were analyzed for the effects of drug treatment or stress. None of the post hoc comparisons between 8-OH-DPAT treatment and stress were statistically significant, suggesting that neither 8-OH-DPAT treatment nor stress affected activity levels significantly during the second activity trial. There was, however, a significant effect of gender on activity for trial 1, $F(1, 142) = 16.3$, $p < 0.0001$, and trial 2, $F(1, 142) = 8.5$, $p < 0.01$, with females recording 22% higher activity counts on trial 1 and 32% higher activity counts on trial 2 compared to males.

DISCUSSION

Sustained stress contributes to physical and mental dysfunction in humans and animals and can lead to cardiovascular disease, gastrointestinal disorders, immunocompetence, depression, and degraded behavioral performance (5,6,16,31,60,70). Our laboratory has been investigating the effects of sustained stress on physiology and behavior to propose novel therapeutics based on knowledge of the mechanisms involved.

The stress paradigm we have utilized effectively models some of the effects of stress that have been reported in humans. For example, sustained stress used in this paradigm decreases food intake, elevates levels of the stress responsive hormones corticosterone and prolactin, disrupts sleep patterning, alters biological circadian rhythms of temperature, and impairs performance on delayed alternation and fixed-interval tasks (4,5,9,10,35–37,39). Similar to the effects of uncontrollable stress in humans (3,16,72), we have found that the effects of stress are generally larger or longer lasting in rats that cannot avoid or terminate stress. Although the paradigm is stressful as judged by the above effects, it is not debilitating. Some measures, such as gross patterning of the estrous cycle in female rats, remain unchanged during this stress paradigm. Most of the measures we have recorded show significant, but transient changes followed by a return to prestress baseline levels. For example, following an initial decrease in food intake and body weight, rats recover prestress feeding rates and gain weight even while under the stress paradigm. Furthermore, the initial disruptions in sleeping patterns and circadian temperature rhythms following stress onset also rapidly return to prestress baseline patterns.

Acute stress causes the release of serotonin as measured by microdialysis (1,57,62) and increases turnover of serotonin in regions of the brain (20,24,29,32). Chronic stress has been reported to desensitize 5-HT_{1A} receptors, possibly due to the increased release of serotonin or through stress-induced increases in the stress hormone corticosterone, which has been shown to modulate 5-HT_{1A} receptors (14,19,49,50,52,56,69,71). These receptor changes are usually limited to specific brain regions. In other brain regions, stress may not have any significant effect or may even increase the number of 5-HT_{1A} receptors (40,51,56). Because of these findings of altered 5-HT_{1A} receptor sensitivity following stress and the efficacy of serotonergic drugs for treating a variety of mental disorders, we performed the experiments described herein to determine whether rats subjected to stress in our chronic stress model would have altered responses to 8-OH-DPAT, a 5-HT_{1A} agonist. We chose the dose of 0.25 mg/kg based on our work with this compound in a water maze task (0.25 mg/kg decreased the rate of acquisition), and from reported studies as a moderate dose representing neither a floor nor ceiling on possible outcomes. We hypothesized that 8-OH-DPAT would increase food intake, increase startle magnitude, and increase locomotor activity in a Figure-8 maze.

Unexpectedly, 8-OH-DPAT, at a dose of 0.25 mg/kg, did not cause the changes in behavior that we predicted from the scientific literature. We saw no effect of 0.25 mg/kg 8-OH-DPAT on locomotor activity as measured in the Figure-8 maze. Nor did we see effects of stress on locomotor activity or a stress 8-OH-DPAT interaction. We did see effects of gender (females more active) and habituation in the second trial of each day compared to the first. But this measure was not useful in testing our hypothesis concerning stress-altered responses to 8-OH-DPAT. 8-OH-DPAT (0.25 mg/kg) did in-

crease the magnitude of the startle response, but stress did not alter this effect nor did stress have an effect of its own on startle. The largest effect of 0.25 mg/kg 8-OH-DPAT was to decrease feeding on the first time of administration. This effect was not seen on subsequent drug administration in nonstressed or stressed rats. Stress by itself with no 8-OH-DPAT also decreased feeding, as we have reported previously. A more detailed discussion of these findings follows.

Food Intake

There was an effect of 0.25 mg/kg 8-OH-DPAT on feeding, although the direction of this change (decreased feeding) is a minority finding in the 8-OH-DPAT literature. In the present experiments, 0.25 mg/kg of 8-OH-DPAT decreased lever pressing for food pellets during the 6-h period after the rats were returned to their cages following activity and startle testing on the first day of 8-OH-DPAT administration. Subsequent 8-OH-DPAT injections on days +1 and +3 in the nonstressed rats decreased food intake less than following the rats' first exposure to 8-OH-DPAT. This finding is not surprising, because a rapid tolerance to the effects 8-OH-DPAT has been reported previously (48). Maswood and Uphouse (1997) found that the effects of 8-OH-DPAT on feeding and hypothermia seen after the first administration of 8-OH-DPAT were reduced or absent following a second administration of 8-OH-DPAT given a week later. Although 8-OH-DPAT has been reported to decrease feeding behavior (7), it has more frequently been reported to increase feeding behavior (8,11,12,25,33,48,62). In other cases, 8-OH-DPAT has had no observable effect on feeding (8,11,13,15,19). These differences could be due to the type of food (e.g., sweetened milk, lab chow, or a high carbohydrate food), the time or route of drug administration, the timing of the food intake interval, the deprivation status of the animal, and/or the dose of 8-OH-DPAT administered (8,11,15,33,46).

Acoustic Startle Response

The serotonergic system has also been implicated in the mediation of the acoustic startle response (22). In the present study, we found that 8-OH-DPAT increased startle magnitude at 100 and 120 dB and decreased latency to peak startle amplitude at 100 dB in both males and females. In addition, 8-OH-DPAT only disrupted prepulse inhibition in males at 120 dB. Other laboratories have also reported that treatment with 8-OH-DPAT increased the magnitude of the startle response significantly (55,67,76) and disrupted prepulse inhibition in male rats (58,65).

One of the diagnostic criteria for posttraumatic stress disorder (PTSD) in humans is heightened response to acoustic startle (17,54,61). Similar abnormalities have been reported in rats that were exposed to footshock [1, 5, or 10 500-ms duration, 0.2–1.4 mA, (21)] or to repeated tailshocks [2-h session consisting of 40 200-ms duration, 2 mA, (61)]. Consequently, we examined whether our model of sustained stress itself would exaggerate the acoustic startle response in these experiments. Stress did not affect any of the startle parameters we measured reliably and did not alter the observed effects of 8-OH-DPAT. However, we may not have seen significant effects of stress because our behavioral measures were taken 24 and 72 h after stress onset, whereas Servatius et al. (1995) found that stress significantly increased startle response approximately 7 days after stress termination.

Locomotor Activity

The effects of 8-OH-DPAT on locomotor activity have not been clearly defined yet. For example, several laboratories have found that 8-OH-DPAT increases activity (12,23,75), decreases activity (18,30), or has no effect on activity (74). In the present study, 8-OH-DPAT did not affect locomotor activity in either male or female rats. The different activity assessment procedures, the time of day the animals were tested, the familiarity of the test apparatus, and the doses of 8-OH-DPAT utilized could account for these differences (34,53,64). High doses of 8-OH-DPAT induce "serotonin syndrome," which includes stereotyped behaviors that might compete with locomotion. However, the dose used in the present experiment was not expected to cause serotonin syndrome, and it was not observed in any of the rats.

Stress did not affect locomotor activity in a Figure-8 maze in the present study. Similarly, restraint stress did not reduce activity in the open field (51). Conversely, restraint stress decreased activity in rats 2 h after restraint (41,64). A more rigorous stress schedule that included 21 days of either shock, food and water deprivation, cold swim, restraint, heat, altering light–dark cycles, switching cage mates, and crowding also significantly decreased exploratory behavior in an open field test (56).

Gender Differences

Because gender differences in serotonin function and performance in animal models of depression have been reported (41), we examined whether differences existed between males and females in locomotor activity, acoustic startle response, and feeding following stress and 8-OH-DPAT treatment. As reported by others, we found that females were significantly more active than males prior to stress or drug treatment (34,51,53,64). Neither stress nor 8-OH-DPAT significantly affected locomotor activity in the present study. Significant differences between males and females also existed for feeding. Males ate significantly more than females, but they weighed 32% more than females. Feeding appeared to be disrupted in both males and females following stress and 8-OH-DPAT administration. Finally, females showed significantly higher acoustic startle magnitudes (100 dB), and were significantly less inhibited by prepulses than males (120 dB) prior to stress or 8-OH-DPAT treatment. Prepulse inhibition was significantly reduced in males following 8-OH-DPAT treatment (120 dB) and stress (100 and 120 dB), but did not change significantly in females. These findings are interesting, because in humans men are more inhibited by prepulses than women (68). Other laboratories, however, have not reported gender difference in prepulse inhibition, magnitude of acoustic startle response, or latency to peak startle amplitude (42,68).

In summary, despite the efficacy of serotonergic drugs to treat depression and reports that chronic stress desensitizes 5-HT_{1A} receptors, no changes in behavioral responses to a serotonergic agonist were seen in chronically stressed rats. A possible reason for the lack of effect of stress on the behaviors tested is that the brain region in which stress-induced desensitization of 5-HT_{1A} receptors has been most frequently observed, i.e., hippocampus, is not the prime neuronal substrate for the behaviors we measured. A better task might be a learning and memory task that relies heavily on hippocampal functioning. Because 8-OH-DPAT has been shown to affect maze performance, a future experiment might compare maze performance in control vs. stressed rats administered 8-OH-DPAT. In addition to different task selection, follow-up experiments should utilize more than one dose of 8-OH-DPAT because 0.25 mg/kg did not affect locomotor activity, and had

only transient effects on food intake. A more robust response to 8-OH-DPAT would make changes in that response (due to stress) more discernable.

ACKNOWLEDGEMENTS

We gratefully acknowledge the technical support provided by Jessica Lin, Nick Tilton, and Maurice Dolberry. This research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals, and adheres to the principles stated in the Guide for the Care and Use of Laboratory Animals, National Academy Press, Washington, DC, 1996. All procedures were reviewed and approved by the WRAIR Animal Use Review Committee. The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense (para 4-3, AR 360-5).

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