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"Paradoxical" Effects of Morphine on Antipredator Defense Reactions in Wild and Laboratory Rats

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BLANCHARD, D. C., A. WEATHERSPOON, J. SHEPHERD, R. J. RODGERS, S. M. WEISS AND R. J. BLANCHARD. *"Paradoxical" effects of morphine on antipredator defense reactions in wild and laboratory rats.* PHARMACOL BIOCHEM BEHAV **40**(4) 819–828, 1991.—In a Fear/Defense Test Battery, measuring defensive reactions to a present, approaching and contacting predator, the highest dose of morphine tested (7.5 mg/kg) reliably reduced vocalization to dorsal contact, to vibrissae stimulation, and to an anesthetized conspecific in laboratory-bred wild *R. norvegicus*. Except for a dose-dependent reduction in flinch/jump reactions to dorsal contact (taps), other defensive behaviors (flight, freezing, etc.) were not reliably altered by morphine treatment (0, 1.0, 2.5, 7.5 mg/kg). Vocalization responses to vibrissae stimulation in wild-trapped *R. rattus* were reliably *increased* following naloxone (1.0 and 10.0 mg/kg) administration, lending support for opiate receptor involvement in the mediation of defensive vocalization. In the Anxiety/Defense Test Battery, measuring defensive reactions to situations associated with a predator (cat) or with cat odor, laboratory rats showed no decrease in defensive behavior with morphine (0, 1.0, 5.0 mg/kg). In direct contrast to the above findings, the effects of morphine treatment in this test battery suggested a generalized increase in defensiveness to noncontacting and nonpainful threat stimuli. These effects included a decrease in time spent near the cat compartment, with a complementary increase in time spent at maximum distance, a decrease in transits between these sections, an increase in crouching, and a decrease in grooming and rearing. This pattern of results suggests that morphine may have two opposing effects on defensive behavior, a generalized enhancement, together with a more specific reduction of responses to tactile or painful stimulation. A very widespread pattern of reliable sex or sex × drug effects in the Anxiety/Defense Test Battery was in good agreement with previous reports of sex differences in these tests, with females generally more defensive than males. Consonant with previous findings, no reliable sex differences were found with the Fear/Defense Test Battery, although several values approached an acceptable level of statistical significance.

Morphine Opioid Opiate Naloxone Fear Anxiety Defensive behavior Sex differences

ENDOGENOUS opioids have been implicated in diverse physiological and behavioral processes (41) and, over the past 15 years, it has become abundantly clear that these peptides play a fundamental role in modulating organismic defense responses to stress (3, 28–34). Biochemical studies have revealed that opioids are released in response to a variety of environmental stressors, including painful (1, 28, 43) and nonpainful (22, 39, 43) threat stimuli. Among other functions, these substances are believed to mediate at least certain forms of stress analgesia (25, 43, 47, 48), a phenomenon which is now considered to be an integral and adaptive component of the defensive repertoire (2, 4, 19, 44). Thus opioid-like analgesia has been reported in rodents exposed to environmental novelty [e.g., (46)], natural predators [e.g., (23)], stress odors [e.g., (20)] and conspecific attack [e.g., (42)].

Exogenous administration of opiates/opioids has provided further support for the involvement of opioid mechanisms in the modulation of defensive behavior patterns. First, although early studies were compromised by the use of sedative doses [for review, (27)], it is now clear that low doses of morphine and related opiate agonists decrease defensive/timid behaviors during social conflict in laboratory mice [for review, (16,26)]; these effects appear to be mu-receptor related since an opposite effect is seen both with kappa agonists (e.g., tifluadom) and the opiate receptor antagonist, naloxone. Secondly, in cats, intracerebral administration of opioid peptides (e.g., D-ALA^{2}met^5-enkephalinamide) has been shown to produce naloxone-sensitive inhibitory effects on defensive reactions elicited by electrical stimulation of periaqueductal gray and medial hypothalamic sites (17,45). Finally, morphine decreases, whereas naloxone increases, separation-induced distress vocalizations in species as diverse as chicks, rats, mice, guinea pigs, dogs and rhesus monkeys [(e.g., (5, 18, 21, 24, 35, 36)].

The present study assesses the effects of morphine on antipredator defense reactions in both wild (*Rattus rattus*) and laboratory (*Rattus norvegicus*) rats. Over the past 5 years, work in

this laboratory has revealed important differences in defensive patterns shown by rats towards a range of nonpainful threat stimuli [for review: (6,12)]. A Fear/Defense test battery [F/DTB: (15)] measures defensive reactions (freezing, flight, defensive vocalization and jump attack) towards present, discrete threat stimuli. In contrast, a more recently developed Anxiety/Defense test battery [A/DTB: (7,10)] measures defensive responses (movement inhibition, inhibition of nondefensive behaviors, risk assessment) to situations in which a predator has been encountered without physical contact but is no longer physically present, or, which include a partial predatory stimulus. These paradigms have already revealed intriguing profiles for compounds with reputed fear-reducing and/or anxiolytic effects, including ethanol (11, 13, 14), benzodiazepines (7, 8, 14), 5-HT_{1A} agonists (9) and scopolamine (40).

EXPERIMENT 1: MORPHINE EFFECTS IN THE FEAR/DEFENSE TEST BATTERY

METHOD

Subjects

Subjects were adult laboratory-born wild *R. norvegicus*. Parents of these animals had been trapped in sugar cane fields near Hilo, HI, and bred in a special facility maintained by the U. of Hawaii Laboratory Animal Services. Subjects were maintained in individual stainless steel cages from weaning until completion of experimental procedures. Each drug-dose group consisted of 12 males and 12 females.

Drug Dose and Administration

Morphine sulphate was dissolved in physiological saline which, alone, served as control. Injections (0, 1, 2.5, and 7.5 mg/kg) were administered IP in a volume of 1 ml/kg body weight, 30 min prior to behavioral testing. Solutions were coded, such that the investigator was blind to the drug status of any animal.

Oval Runway Apparatus and Procedures

Since both the apparatus and procedures for the F/DTB have been reported previously [Blanchard et al., (6,7)], only an abbreviated description is given here. The oval runway was a 6×2 m area with rounded ends, divided down the middle by a plywood partition 4 m in length, marked at 1 m intervals to facilitate recording of distances run.

Five-min pretest. The subject was placed in the runway, and line crossings were recorded during a 5-min pretest period.

Discriminated avoidance. The experimenter made 5 approaches at a speed of half a meter per second toward the subject, until contact was recorded, or, the subject ran away. If the subject avoided by running away, avoidance distance (experimenter-subject distance when flight occurred) and the distance fled (escape distance) were recorded.

Flight duration. The experimenter approached the subject at a speed of roughly 1.5 to 2 meters per second, and, using a stopwatch, recorded the time it took to chase the subject a distance of 36 meters. If flight did not occur, a chase time of 300 seconds was assigned and the trial was terminated.

Inescapable Runway Apparatus and Procedure

Closing of partitions at both ends of a straight segment of the oval runway produced a 4×1 m straight runway. In the runway, the experimenter made 5 approaches toward the subject at a speed of 0.5 m/s, pausing for 30 s at distances of 4, 3, 2, 1 and 0.5 m from the subject. Subject freezing was recorded at each distance.

Proximal Testing Apparatus and Procedure

The following defensive tests were conducted while the subject was in an aluminum barrel, 50 cm in diameter and 120 cm in height.

Dorsal contact. The subject was lightly tapped on the dorsal flank with a wooden dowel and Jump/Flinch reactions were scored on a 1–5 rating scale, where 1 represented a local flinch reaction, and 5, a rapid jump with all 4 limbs leaving the floor. Vocalization to dorsal contact was also recorded. Four trials were made and scores for each behavior summed over these trials.

Vibrissal stimulation. Two adjacent circular brushes mounted on a rod were used to stimulate the subject's vibrissae, in a series of 4 trials. Defensive attack behaviors, boxing, biting, vocalizing, and jump attacks, to vibrissal stimulation were recorded.

Anesthetized conspecific. A terminally anesthetized conspecific was moved toward the subject (snout forward) at a rate of 5 cm per second, until contact occurred. Boxing, biting, vocalizing, and jump attacks toward the head and snout of the anesthetized conspecific were recorded during 4 trials.

Reaction to handling. The subject's defensiveness in response to an attempt by the experimenter to pick it up was rated on a scale from 0 (no defensiveness) to 5 (no pickup possible) during a single pickup attempt.

RESULTS

Table 1 presents the results of the initial oval runway tests, and the proximal tests, for subjects at the various dose levels.

Oval Runway

Line crossings in five-min pretest. ANOVA for line crossings in the 5-min pretest period indicated no reliable effects of dose. The effects of sex approached but failed to reach, $F(1,22) = 4.19$, $0.10 > p > 0.05$, an acceptable level of statistical significance, with females making an average of 46.25 line crossings, and males, 30.77.

Flight and avoidance to the experimenter. Sex and dose effects on percent avoidance of the experimenter approached, but failed to reach, an acceptable level of statistical significance [$F(1,22) = 3.81$ and $F(3,66) = 2.23$, respectively, $0.10 > p > 0.05$ in each case]. Females made an average of 4.15 avoidances, and males, 3.54.

Dose effects on flight duration were not reliable, but sex effects approached an acceptable level of statistical significance, $F(1,22) = 3.59$, $0.10 > p > 0.05$, with females running the required 36 m distance in an average of 40.60 s, while males required an average of 68.22 s.

Sex and dose effects on avoidance distance and escape distance were not reliable.

Inescapable Runway

The effect of decreasing distance between the experimenter and the subject was highly reliable for the freezing measure, $F(4,45) = 38.84$, $p < 0.000001$, with freezing declining sharply as contact approached. Drug and sex effects on this measure were not reliable.

Proximal Testing

Dorsal contact. Dose effects on flinch/jump reactions to dorsal contact were reliable, with flinch/jump levels declining in a dose-dependent manner, $F(3,66) = 4.42$, $p < 0.01$. Sex effects also

TABLE 1

MORPHINE IN THE FEAR/DEFENSE TEST BATTERY

Dose	Saline		1		2.5		7.5	
Line Crossings	37.17	(4.52)	34.12	(4.44)	42.33	(5.33)	40.42	(5.94)
Percent Avoidance	74.17	(6.86)	79.17	(5.31)	67.50	(6.23)	86.60	(3.93)
Avoidance Distance	1.75	(0.24)	1.40	(0.17)	1.59	(0.15)	1.18	(0.12)
Escape Distance	1.04	(0.17)	1.23	(0.19)	1.06	(0.13)	1.37	(0.18)
Flight Duration	59.23	(10.17)	53.95	(8.65)	60.29	(12.14)	44.16	(7.76)
Freezing Duration	71.33	(8.53)	77.25	(12.04)	74.58	(11.44)	84.50	(12.72)
Dorsal Contact Reaction	7.92	(1.11)	6.71	(0.93)	5.67	(0.93)	4.29	(0.69)*
Vibrissae Boxing	3.92	(0.37)	3.75	(0.26)	3.08	(0.43)	3.17	(0.39)
Vibrissae Biting	1.12	(0.33)	1.67	(0.43)	1.00	(0.33)	0.83	(0.30)
Vibrissae Jump Attack	0.12	(0.12)	0.42	(0.20)	0.25	(0.17)	0.04	(0.04)
Conspecific Boxing	3.21	(0.34)	3.54	(0.32)	2.50	(0.43)	2.58	(0.44)
Conspecific Biting	1.46	(0.44)	1.46	(0.41)	1.25	(0.45)	0.79	(0.32)
Conspecific Jump Attack	1.17	(0.41)	1.08	(0.35)	0.75	(0.33)	0.33	(0.22)
Rated Defensiveness	2.59	(0.20)	2.61	(0.22)	2.38	(0.19)	2.09	(0.16)*

Effects of morphine (0, 1.0, 2.5 and 7.5 mg/kg) in the oval runway test and the proximal tests of the Fear/Defense Test Battery. Data given are mean and (standard error) for each measure. *Indicates $p<0.05$.

approached, but failed to reach, an acceptable level of statistical significance, $F(1,22)=3.22$, $0.10>p>0.05$.

Figure 1 presents vocalization to three stimuli, dorsal contact, vibrissae brush, and anesthetized conspecific, for rats under the various morphine doses. Dose effects on vocalization to dorsal contact were reliable, with vocalization levels declining in a dose-dependent manner, $F(3,66)=5.15$, $p<0.01$.

Vibrissae brush. Dose effects on boxing to brush stimulation of the vibrissae approached, but failed to reach, an acceptable level of statistical significance, $F(3,66)=2.52$, $0.10>p>0.05$. Dose effects on bites to vibrissae brush stimulation were not reliable, nor were jump attacks to this stimulus.

At the highest dose of morphine, vocalization scores to tactile stimulation of the vibrissae consisted largely of zeros and thus were not normally distributed. A Wilcoxon test indicated that the 7.5 mg/kg group made reliably fewer vocalizations than the saline group, $t(6,24)=0$, $p<0.05$. No other differences were reliable.

Anesthetized conspecific. Dose and sex effects on boxing and bites to the anesthetized conspecific were not reliable. Both effects approached, but failed to reach an acceptable level of statistical significance for jump attacks to the anesthetized conspecific [$F(3,66)=2.62$ for dose and $F(1,22)=3.68$ for sex, $0.10>p>0.05$ in either case]. However, dose effects on vocalization to this stimulus were reliable, with vocalization declining in a dose-dependent manner, $F(3,66)=4.75$, $p<0.01$.

Attempted pickup. Dose effects on reactions to attempted pickup were reliable, $F(3,66)=3.61$, $p<0.05$ with ratings declining in a dose-dependent manner.

EXPERIMENT 2: EFFECTS OF NALOXONE IN THE F/DTB

The lack of effects of morphine on defensive behavior, except for vocalization, in the F/DTB was surprising. To further investigate opiate effects on these behaviors, we used 1.0 and 10.0 mg/kg of naloxone, an opiate receptor antagonist, in the same set of tasks.

METHOD

Subjects

Subjects were 12 male and 10 female singly housed adult wild rats (*R. rattus*) trapped in sugar cane fields near Hilo, HI.

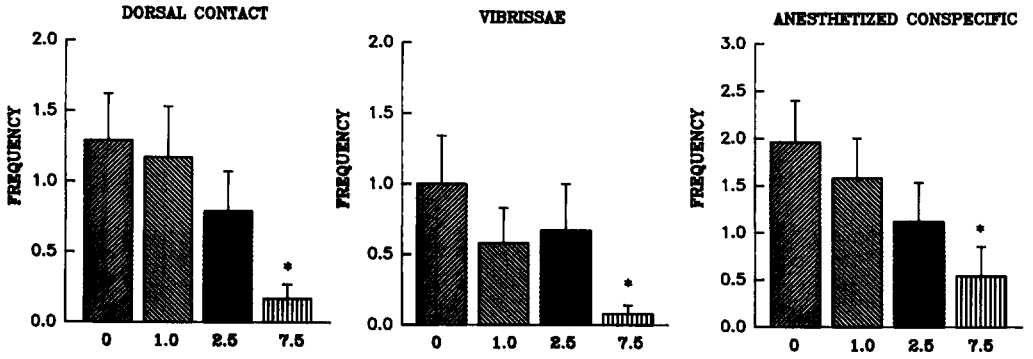

FIG. 1. Effects of morphine (0, 1.0, 2.5 and 7.5 mg/kg) on sonic vocalization to dorsal taps, to brushing of the vibrissae, and to an anesthetized conspecific, in the Fear/Defense Test Battery. *$p<0.05$ versus saline.

TABLE 2

NALOXONE IN THE FEAR/DEFENSE TEST BATTERY

Dose	Saline		1 mg/kg		10 mg/kg	
Line Crossings	39.14	(6.14)	37.77	(5.40)	40.27	(5.43)
Percent Avoidance	99.09	(0.01)	94.55	(0.04)	97.27	(0.03)
Avoidance Distance	2.57	(0.17)	2.54	(0.19)	2.65	(0.17)
Escape Distance	1.21	(0.14)	1.13	(0.16)	1.16	(0.15)
Flight Duration	17.85	(1.91)	28.69	(12.93)	30.07	(12.89)
Freezing Duration	144.64	(5.24)	146.68	(7.37)	130.18	(8.13)
Dorsal Contact Reaction	15.23	(0.75)	14.05	(0.59)	14.00	(0.76)
Vibrissae Boxing	3.91	(0.06)	3.68	(0.15)	3.91	(0.06)
Vibrissae Biting	2.41	(0.29)	1.91	(0.37)	1.73	(0.34)
Vibrissae Jump Attack	1.45	(0.34)	1.00	(0.28)	0.59	(0.17)
Conspecific Boxing	3.91	(0.06)	3.95	(0.05)	3.91	(0.06)
Conspecific Biting	2.91	(0.30)	3.18	(0.29)	3.27	(0.22)
Conspecific Jump Attack	0.64	(0.20)	0.95	(0.27)	0.50	(0.17)
Rated Defensiveness	4.09	(0.08)	4.12	(0.12)	4.21	(0.06)

Effects of naloxone (0, 1.0, 10.0 mg/kg) in the oval runway test and the proximal tests of the Fear/Defense Test Battery. Data given are mean and (standard error) for each measure. *Indicates $p<0.05$.

Procedures

Apparatus and procedures used, including statistical analyses, were similar to those used in Experiment 1. Due to an error on the scoring sheets, the vocalization to dorsal contact measure taken in the morphine study was not taken in the naloxone study.

RESULTS

Table 2 presents the results of the initial oval runway tests, and the proximal tests, for subjects at the various dose levels.

Oval Runway

Line crossings in five-min pretest. ANOVA for line crossings in the 5-min pretest period indicated no reliable effects of dose, sex, or time. However, the triple interaction, S × D × T was reliable, $F(8,168)=4.51$, $p<0.05$, apparently reflecting very divergent effects of time in the situation for males and females under the saline dose: females became more active over time, while males were initially more active, but quickly declined. These differences were abolished with both naloxone doses.

Flight and avoidance to the experimenter. No reliable effects of dose, sex, time, or interactions of these, were found for the avoidance distance, the number of avoidances, or the escape distance measures. The effect of sex on flight duration approached significance, $F(1,20)=3.58$, $0.10>p>0.05$, but there were no reliable drug or interaction effects on this measure.

Inescapable Runway

The effect of decreasing distance between the experimenter and the subject was highly reliable for the freezing measure, $F(5,100)=22.59$, $p<0.000001$, with freezing declining sharply as contact approached. In addition, the drug effect on this measure approached, but failed to reach, an acceptable level of statistical significance, $F(2,40)=2.53$, $0.10>p>0.05$, with the higher naloxone dose associated with decreased levels of freezing. Sex and interaction effects were not reliable.

Proximal Testing

Dorsal contact. Both sex, $F(1,20)=2.94$, $p=0.10$, and sex × drug, $F(2,40)=2.47$, $0.10>p>0.05$, effects on rated reactions to dorsal contact approached, but failed to reach, an acceptable level of statistical significance. Drug and other interaction effects on this measure were not reliable.

Vibrissae brush. Drug, sex and sex × drug effects on boxing to vibrissae contact all failed to reach an acceptable level of statistical significance.

Naloxone effects on sonic vocalization to the vibrissae brush and the anesthetized conspecific are presented in Fig. 2. Drug effects on vocalization to tactile stimulation of the vibrissae were reliable, $F(2,40)=5.75$, $p<0.01$: both the 1 mg/kg and the 10 mg/kg groups showed reliably more vocalization than the saline group (Newman-Keuls, $p<0.01$ in both cases). Sex and sex × drug effects were not reliable.

Drug, sex and sex × drug effects on bites to vibrissae brush stimulation were not reliable. However, both sex and drug effects on jump attack approached an acceptable level of statistical significance [$F(1,20)=3.13$, for sex, and $F(2,40)=2.61$, for drug effect, $0.10>p>0.05$ in both cases].

Anesthetized conspecific. Dose and sex effects on boxing, bites, jump attacks, and vocalization to the anesthetized conspecific were not reliable. However, the dose effect on conspecific jump attack approached an acceptable level of statistical significance, $F(2,40)=2.96$, $0.10>p>0.05$. Sex × drug dose effects

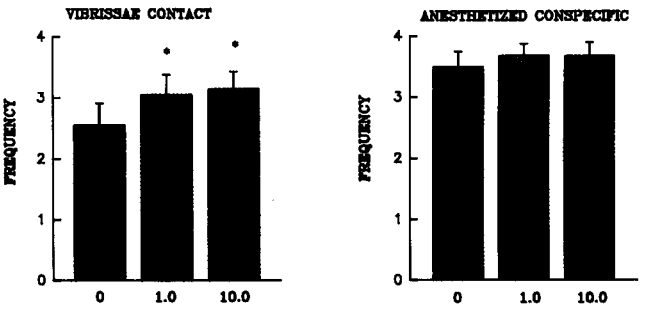

FIG. 2. Effects of naloxone (0, 1.0, and 10.0 mg/kg) on sonic vocalization to brushing of the vibrissae, and to an anesthetized conspecific, in the Fear/Defense Test Battery. *$p<0.05$ versus saline.

were statistically significant for boxing, $F(2,40)=3.49$, $p<0.05$, and for jump attacks, $F(2,40)=4.91$, $p<0.05$. Females tended to make many more jump attacks at the anesthetized conspecific than did males under the saline condition, but these differences disappeared at the higher drug dose levels, with an opposite picture (more male boxing under saline) for the box measure. Since boxing and jump attacks are to some degree incompatible during these short trials with the anesthetized conspecific (the animal can do both, but it has to be quick), it is possible that these opposite s × d interactions may reflect a partial disruption of one response by the other.

Attempted pickup Dose, sex, and interaction effects on reactions to attempted pickup were not reliable.

EXPERIMENT 3: MORPHINE IN THE ANXIETY/DEFENSE TEST BATTERY

In contrast to the Fear/Defense Test Battery, which involves (with the possible exception of the pretest line-crossings measure [see Blanchard et al. (8)] direct confrontation of the subject with a threatening stimulus, an Anxiety/Defense Test Battery has been devised to measure defensive reactions to situations associated with threat or partial, unconditioned threat stimuli such as the odor of a cat. The classic anxiolytic, diazepam, has been shown to produce very different effects on these measures (7), in comparison to defensive behaviors to a present, discrete threat stimulus in the F/DTB (8). Thus Experiment 2 involved an assessment of the effects of morphine on tests similar to those used in the A/DTB.

METHOD

Subjects

Subjects were singly housed adult Long-Evans hooded rats from breeding stock maintained by the University of Hawaii Laboratory Animal Services. Each cat-exposed, drug-dose group consisted of 8 males and 7 females, while the saline, no-cat control group was composed of 8 males and 5 females.

Drug Dose and Administration

Morphine sulphate was dissolved in physiological saline which, alone, served as control. Injections (0, 1.0 and 5.0 mg/kg) were administered IP in a volume of 1 ml/kg body weight, 30 min prior to behavioral testing. Solutions were coded, such that the investigator was blind to the drug status of any animal.

Test Apparatus and Procedures

The apparatus and procedures of the A/DTB have been described in detail elsewhere (Blanchard et al., in press). Thus only a very brief description is given here.

Cat exposure apparatus. The test apparatus used in the first (activity/freezing) and second (eat/drink) tests consisted of two side-by-side subject chambers, fronting on a cat compartment. Laterally mounted videocamera provided a videorecord of the subject in that chamber, and subject movements were monitored by 5 photocells mounted at equal distances along the inner, opaque Plexiglas, walls. A food hopper and drinkometer could be made available by removal of gates.

Proxemic and activity testing. Each subject was run twice in the cat exposure apparatus, with the two sessions 8–12 days apart. For the initial test session measuring proxemics and activity, subjects were individually placed in each subject compartment. Following a 5-min precat period, the cat was placed in the cat compartment for 5 min, with a 20 min postcat period. Measures were summed in four, five-min blocks, or two, 10-min blocks for proxemic/activity measures. No-cat vehicle control animals simply experienced opening of the cat compartment doors at the appropriate times. Ratings made every 30 s from the video record provided measures of lying, crouching, rearing, locomotion, and grooming. Proxemic location was measured by a digitizer, which divided the length of the subject compartment into thirds, measuring the animal's location in the segment near the cat compartment, in the midsection of the box, or far from the cat compartment. Transits involved movement from one such section to another.

Eat/drink testing. In the 8–12 day interval between the first and second tests in this apparatus, subjects were familiarized with a highly preferred chocolate cereal (1 g, finely crushed) on three occasions. Their water bottles were removed 24 hours prior to testing, but lab chow was available at all times.

On the test day, subjects received the same injections as in the initial test, and were placed in the subject compartments. No food or water was available during a 5-min precat period in the test apparatus, but immediately after the cat was presented in the cat compartment, 1 gram of finely crushed chocolate cereal in a petri dish and a water bottle were placed in each subject compartment. After the 5-min cat period, subjects were monitored for an additional 20 min. The cat was not presented for the no-cat (vehicle) control subjects, but the apparatus was opened and closed at the appropriate times and the food and water presented after the initial door opening/closing. Measures taken were eat frequency and duration and drink frequency.

Cat odor apparatus. The cat odor apparatus was a box 120 cm long, and 15 cm in width, with a 9×9 cm, cloth-covered, wood block at one end. This block was saturated with cat odor for the experimental condition and untreated for the control condition. The front of the box was a clear Plexiglas sheet to allow video access.

Cat odor testing. Subjects were run in the cat odor box 5–14 days after the eat/drink test. Each subject received the same injection as in the two previous tests and was placed in the cat odor apparatus for a 10 min session. Frequencies and/or durations were measured for stretch approach [a measure of defensiveness: Blanchard et al. (12)], curved back (nondefensive) locomotion, contact with the odor stimulus, grooming, and rearing (measured separately when subject was standing on, or off, the cat odor stimulus).

RESULTS

Proxemic/Activity Test

Figure 3 presents results of the proxemic/activity tests.

Location near cat compartment. Comparison of the saline groups indicated a reliable decline in time spent near the cat compartment by cat-exposed animals, $F(1,23)=17.91$, $p<0.001$. No other main effects or interactions were significant.

Analysis of the cat-exposed groups failed to indicate significant main effects of sex or dose. However, dose × time, $F(6,114)=3.72$, $p<0.002$, and sex × dose × time, $F(6,114)=3.38$, $p<0.005$, effects were reliable, with a reliable main effect for dose, $F(2,38)=4.64$, $p<0.02$, only in the first five min (post 1) period, with reduced time near the cat compartment for animals receiving both 1 and 5 mg/kg morphine (Newman-Keuls, $p<0.05$). While morphine effects on females' time near the cat compartment were not reliable, this measure was significantly reduced in morphine-treated males during the post 1, $F(2,21)=4.99$, $p<0.02$, period. Newman-Keuls analysis indicated a sig-

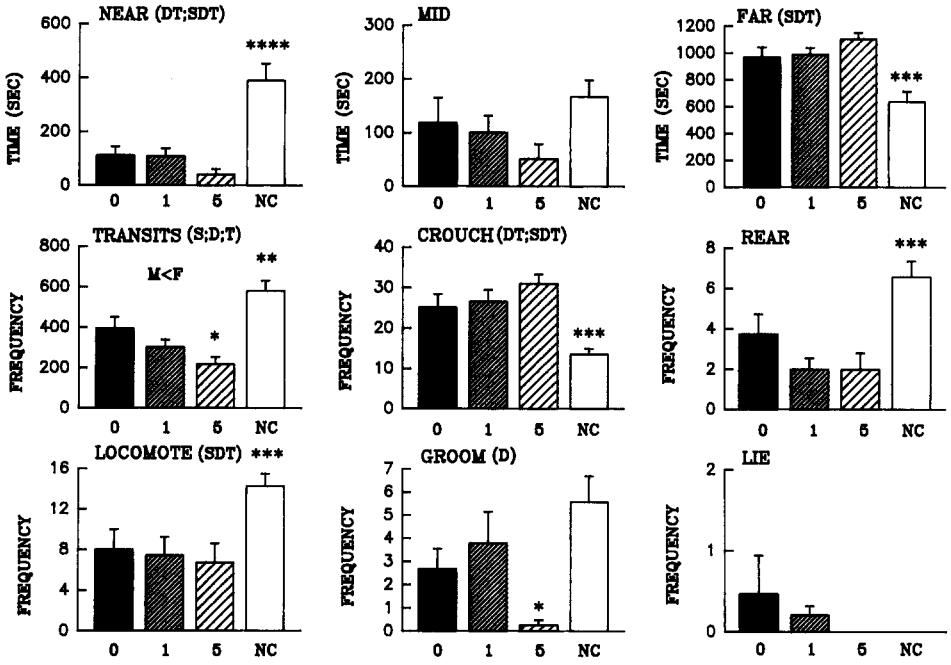

FIG. 3. Effects of morphine (0, 1.0 and 5.0 mg/kg) on location (near, mid, or far) re the cat compartment, transit to and from the cat compartment, and specific behaviors in a chamber adjacent to the cat compartment, in the proxemic/activity test. Cat-exposed groups: S;D;T = main effect for sex/dose/time SD/SDT interaction. M<F = males lower than females. All treatment groups: ****$p<0.001$, ***$p<0.01$, **$p<0.02$, *$p<0.05$ vs. saline (cat-exposed).

nificant reduction in time spent near the cat compartment in the post 1 period for males receiving 1 or 5 mg/kg morphine (Newman-Keuls, $p<0.05$).

Midchamber location. There were no reliable effects of either cat exposure or morphine treatment on time in the midsection of the activity box.

Location far from cat compartment. There was a significant effect of cat exposure for saline-treated animals, with more time spent in the far location following cat presentation, $F(1,23) = 8.74$, $p<0.01$. No other main effects or interactions were significant.

The cat-exposed groups failed to show reliable main effects of sex or dose. However, the sex × dose × time interaction was reliable, $F(6,114) = 2.88$, $p<0.02$, reflecting a data profile of high cat avoidance by males at 5.0 mg/kg morphine, while females appeared to be unaffected at all doses.

Transits. Comparisons of saline groups indicated a reliable decline in transits with cat exposure, $F(1,23) = 6.92$, $p<0.02$. Time following exposure also produced a reliable effect, $F(3,69) = 16.55$, $p<0.0001$, with transits decreasing as time after cat exposure progressed. Sex and interaction effects were not significant.

Analysis of the cat-exposed groups indicated significant main effects for sex, $F(1,38) = 4.02$, $p<0.05$, dose, $F(2,38) = 4.34$, $p<0.02$, and time, $F(3,114) = 25.91$, $p<0.0001$. A significant decrease in transits at 5.0 mg/kg morphine (Newman-Keuls: $p<0.05$), suggested potentiation of this response to cat exposure. The significant main effect for sex was due to generally fewer transits in males, while the significant time effect reflects a decrease in transits with increasing time after cat exposure.

Lie. Kruskal Wallis tests (lie data were nonparametric) failed to indicate reliable effects of cat exposure or morphine treatment on lying.

Crouch. Comparison of saline groups indicated a reliably greater crouching with cat exposure, $F(1,23) = 8.93$, $p<0.01$. No other effects were reliable.

Analysis of the cat-exposed groups failed to indicate significant main effects for either sex or dose. However, there were significant dose × time, $F(2,38) = 3.73$, $p<0.05$, and sex × dose × time, $F(2,38) = 3.53$, $p<0.05$, interactions. The data profile suggests that both male and female subjects treated with 5.0 mg/kg morphine tend to exhibit higher levels of crouching in the initial ten minute period following cat exposure. In the final observation periods (10–20 min postcat), this effect is maintained in only the male subjects.

Rear. For the saline groups, there was a significant decrease in rearing with cat exposure, $F(1,23) = 7.41$, $p<0.01$. No other effects were reliable.

For the cat-exposed groups, there were no reliable effects on rearing behavior.

Locomote. For the saline groups, there was a reliable decrease in locomotion with cat exposure, $F(1,23) = 6.79$, $p<0.02$. No other effects were reliable.

Analysis of cat-exposed groups indicated a significant sex × dose × time interaction, $F(2,38) = 3.98$, $p<0.05$, associated with a significant sex effect, $F(1,38) = 7.40$, $p<0.01$, and sex × dose interaction, $F(2,38) = 3.96$, $p<0.05$, in the post 2 (10–20 min postexposure) period: only females showed increased locomotion at the higher dose level, later in the test period.

Groom. For the saline groups there was no reliable effect of cat exposure on grooming. However, a significant main effect for sex, $F(1,23) = 5.64$, $p<0.05$, reflected a lower level of grooming in females.

For the cat-exposed groups, there was a reliable dose effect, $F(2,38) = 3.75$, $p<0.05$, with a significant decrease in postcat

TABLE 3

EFFECTS OF MORPHINE ON EATING/DRINKING IN RATS FOLLOWING CAT-EXPOSURE

Dose (mg/kg)	Eating Frequency	Eating Duration	Drinking Frequency
0	39.67	101.43	490.93
1.0	50.14	153.82	160.29
5.0	48.67	234.99	74.47
No Cat	39.58	160.61	511.67

Data are expressed as mean totals for 20 min postcat period.

grooming behavior at 5.0 mg/kg morphine compared with 1.0 mg/kg morphine (Newman-Keuls: $p<0.5$). However, no group was reliably different from control.

Eat/drink test. Table 3 presents morphine effects on frequency and duration of eating, and frequency of drinking, in the Eat/Drink test.

Frequency of eating. Comparison of the saline groups indicated that, although cat exposure did reduce eat frequency during the 5-min period when the cat was present $F(1,23)=5.91$, $p<0.05$, this effect was not reliable in the 20-min period after the cat had been removed.

Duration of eating. In comparison of the saline groups, cat exposure failed to produce a reliable effect on eating duration. However, there was a significant sex × time interaction, $F(3,69)=3.45$, $p<0.05$, with a higher level of eating in females during the first 5 minutes after cat presentation, $F(1,23)=4.42$, $p<0.05$. No other effects were reliable.

Analysis of the cat-exposed groups failed to indicate any reliable effects of drug treatment on feeding durations.

Frequency of drinking. Data for the saline groups failed to indicate any reliable effect of cat exposure on frequency of drinking, the only drinking measure taken.

The effect of morphine treatment for the cat-exposed groups approached, but just failed to reach, an acceptable level of statistical significance, $F(2,38)=3.20$, $p>0.051$. The data profile suggested a sharp (84% at the high dose) decrease in drinking with morphine treatment.

Cat Odor Data

Table 4 presents behaviors in the cat odor test for subjects not exposed to the cat odor stimulus, and, as a function of morphine dose for subjects exposed to the stimulus.

Frequency/duration of stretch approach/attend. Comparisons of exposed/nonexposed groups revealed significant increases in stretch-approach/attend frequency, $F(1,22)=14.48$, $p<0.002$, and duration, $F(1,22)=9.35$, $p<0.01$, with cat-odor exposure, together with reliable effects of sex on both frequency, $F(1,22)=6.34$, $p<0.02$, and duration, $F(1,22)=9.35$, $p<0.05$; and reliable sex × odor interactions for both frequency, $F(1,22)=5.27$, $p<0.05$, and duration, $F(1,22)=4.20$, $p<0.05$. The two latter findings reflect (a) generally higher stretch approach/attend frequencies/durations in females and (b) a more substantial increase in these behaviors with exposure to cat odor in females compared with males.

ANOVA for the odor-exposed groups failed to indicate reliable effects for dose or sex × dose. However, analysis did reveal a significant main effect of sex for stretch approach/attend frequency, $F(1,36)=6.59$, $p<0.02$, and duration, $F(1,36)=5.95$, $p<0.02$, reflecting higher levels of stretch approach/attend in females.

Frequency/duration of curved back approach. Cat odor presentation produced reliably lower frequencies of curved back approach frequency, $F(1,22)=9.35$, $p<0.01$, and duration, $F(1,22)=8.10$, $p<0.01$. No other main effects or interactions were significant.

Data for the cat odor groups failed to indicate any reliable effects of drug or sex on curve back frequencies or durations.

Contact frequency/duration. There were no reliable effects of either cat odor presentation or morphine treatment on contact frequency, but cat odor reliably reduced duration of contact with the odor stimulus, $F(1,22)=5.44$, $p<0.05$. No other reliable effects were obtained.

Frequency/duration of grooming. ANOVA failed to indicate effects of either cat odor or morphine treatment on grooming frequencies or durations.

Duration rear: off stimulus. The cat odor stimulus failed to produce a reliable main effect on the duration of rearing, off the stimulus block. However, the main effect of sex was significant, $F(1,22)=11.38$, $p<0.005$, with females rearing more often. Also, the sex × odor exposure interaction was reliable, $F(1,22)=4.82$, $p<0.05$, reflecting a general increase in rearing for males following odor presentation (Newman-Keuls: $p<0.05$), whereas females, who displayed much higher control levels, were not affected by odor.

Analysis of morphine treatment data indicated a significant effect of dose, $F(2,36)=4.59$, $p<0.02$, due to a decrease in

TABLE 4

EFFECTS OF MORPHINE ON BEHAVIORAL RESPONSES TO CAT ODOR PRESENTATION

Dose (mg/kg)	Stretch Approach Freq.	Stretch Approach Dur.	Curved Back Freq.	Curved Back Dur.	Contact Freq.	Contact Dur.	Groom Freq.	Groom Dur.	Rear Off Dur.	Rear On Dur.
0	9.86	35.00	10.86	34.57	9.86	78.93	3.57	54.79	46.21	2.86
1.0	8.21	27.43	11.71	38.29	11.07	92.64	2.93	47.93	40.57	1.43
5.0	8.57	40.29	8.50	31.14	5.43	56.64	2.57	37.43	31.86	1.07
No Cat	1.33	3.75	12.83	47.83	11.00	153.25	3.08	66.92	38.00	4.00
Effects $p<0.05$	odor; sex; sex × odor	odor; sex; sex × odor	odor	odor		odor			sex; dose; sex × odor	

Data are presented as means.

rearing at 5.0 mg/kg (Newman-Keuls: $p<0.05$). No other effects on this measure were significant.

Duration rear: on stimulus. ANOVA failed to confirm any effects of cat odor exposure or morphine treatment on rearing on the block.

GENERAL DISCUSSION

Sex Differences

Sex differences in defensive behaviors have emerged as a consistent feature of the A/DTB (7, 13, 14). In contrast, previous F/DTB studies (8, 9, 15) have not revealed reliable sex effects. The results of the present series provide further detail on these differences, in the two test batteries.

The major difference of these and previous studies is that, while none of the effects of sex on the measures of either the present morphine or naloxone F/DTB studies reached an acceptable level of statistical significance, it might be noted that sex effects approached significance ($0.10>p>0.05$) on 5 of these measures in the morphine study, and on 3 measures of the naloxone study. The pretest (involving a novel environment briefly associated with the presence of the experimenter) showed a sex effect in the morphine study, and a triple interaction (s × d × time), which was reliable, in the naloxone study. In the morphine study, female scores were higher on two of the oval runway measures (percent avoidance and flight duration) and one of these, flight duration, was also higher for females ($0.10>p>0.05$) in the naloxone study. Two of the measures to close-in or contacting threat stimuli approached significance in the morphine study, and two in the naloxone study, with one measure (reactions to dorsal contact) tending to be higher for females in both. This consistency, that the same measures tended to produce (marginal) sex differences in both the morphine and naloxone studies, provides an additional, albeit fairly minor, indication of similarity between the dynamics of the defense systems in wild *R. norvegicus* and *R. rattus*, the subjects of these two studies.

The consistency of these patterns between the morphine and naloxone studies also suggests that the enhanced defensiveness of female rats, previously noted only in the A/DTB (7, 13, 14), may be more general. As one possible alternative interpretation, the finding of stronger (i.e., more often reliable) sex differences in the latter tests may reflect the fact that laboratory rats rather than wild rats have been used in those tests, and that (perhaps because of ceiling or floor effects) sex differences in defensiveness may be more likely to be pronounced in preparations reflecting moderate, as opposed to very high levels of defensive reactivity.

In the present A/DTB study, indications of higher defensiveness for females continued to appear. For example, females showed reliably less grooming, and reliably greater frequencies and durations of stretch attend/approach, and of rearing (while not contacting the cat odor stimulus). Since grooming declined reliably with cat exposure, while frequency and duration of stretch attend/approach increased when the cat odor stimulus was present, this pattern of findings is consonant with previous results, indicating that females show more of the same reactions that are elicited in both sexes by the presentation of a threatening stimulus. Such findings, and the remaining sex differences of the present A/DTB study, are clearly compatible with the view that females, in these tests involving potential threat, are more reactive than males.

Drug Effects

Reliable morphine effects, each involving decreased responsivity at the highest dose, were obtained for vocalization to dorsal contact, vibrissae stimulation and vocalization to an anesthetized conspecific, startle reactivity to dorsal contact and ratings of defensiveness to an attempted pick up.

These measures appear to involve two common factors; first, vocalization, with all vocalization measures significant. A second common factor was that of direct, tactile contact by the eliciting stimulus. The eliciting stimuli in each vocalization test were tactile, including the anesthetized conspecific which was brushed against the subjects' vibrissae, while startle to dorsal contact and rated defensiveness to pick up both involved tactile stimuli. This factor is emphasized by two additional measures involving tactile contact on which morphine dose effects approached, but failed to reach ($0.10>p>0.05$) an acceptable level of significance: boxing to vibrissae stimulation and jump-attack to the anesthetized conspecific. Thus 5 of the 11 measures of reactivity to direct tactile stimulation (involving each type of tactile stimulus presented) were reliably reduced for morphine-treated animals, while 2 more measures approached significance, again showing a decline at higher morphine doses.

In contrast, for the 6 measures not involving tactile contact (line crossings, percent avoidance, avoidance distance, escape distance, flight duration, and freezing) morphine effects were not reliable, although the morphine effect on percent avoidances again approached statistical significance.

The naloxone findings agree well with this profile, suggesting great specificity of opiate effects on defense; the single significant naloxone effect was increased vocalization to vibrissae stimulation. It might be noted that the wild-trapped rats of the naloxone study showed a somewhat higher level of vocalization in these tests than did the laboratory-bred wild rats of the morphine study. This difference, which may reflect self-selection of less defensive animals for breeding in proximity to humans, nonetheless leaves first generation laboratory-bred wild rats considerably more defensive than are laboratory rats (15). However, the especially high level of wild rat vocalizations to the anesthetized conspecific (notably higher than those to vibrissae stimulation) may well have created a ceiling effect which precluded substantial naloxone increases in this measure, leaving open the possibility that naloxone effects on vocalization measures might generally be opposite to those of morphine. Naloxone effects on freezing also approached an acceptable level of statistical significance, which was associated with reduced freezing at the higher dose level.

In the A/DTB (cat exposure apparatus), morphine decreased time near the cat area, and also increased time in the segment far from the cat area, in the initial time period after cat exposure. Since an intermediate section was available, these two measures were independent, and in each case morphine effects were similar to the effects of cat exposure. Morphine also decreased the number of transits among the various sections of the apparatus, an effect which again was similar to that of cat exposure. Crouching, which increased with cat exposure, increased also with morphine, a finding in agreement with the apparent reduction in freezing with the higher naloxone dose. Grooming declined with morphine and, while cat exposure did not reliably affect grooming in the present studies, it has done so in previous work using these tests (7,13). These findings, each of which involves a morphine effect similar to a cat exposure effect, strongly suggest that morphine increases defensive reactivity to the cat. It is notable that the reduced transits and grooming and increased crouching might be interpreted as indicating a possibly sedative effect of morphine, as opposed to an anxiolytic effect. However, this interpretation is not compatible with the finding that lying was not affected by morphine, or by the reliable triple interaction for locomotion, reflecting increased locomotion in

females with the highest morphine dose, later in the test session.

Morphine produced no reliable effects in the eat/drink test, although the decreased drink frequency with morphine, a phenomenon suggesting an anxiogenic effect, was very close to an acceptable level of statistical significance. In the cat odor test, only a single reliable difference was obtained, for rearing off the cat odor stimulus, which declined at the higher (5.0 mg/kg) morphine dose. No main effect of cat odor stimulus was found for rearing, so this measure is difficult to interpret, but the significant sex × cat odor exposure interaction (see discussion of sex differences) suggests that such rearing may be related to risk assessment, and that, in this context, decreased rearing with morphine is consonant with a view of increased defensiveness to the cat odor stimulus.

These findings thus provide a consistent view of morphine effects on defensive behaviors of rats to a potential threat stimulus. This view, that morphine *increases* defensiveness to situations associated with a cat, or with partial cat (odor) stimuli, is contrary to the general view that morphine, and opiate/opioid agonists generally, *decrease* defensiveness (see the Introduction for review). One possible explanation may involve potential, as opposed to actual threat, in that the present Experiments 1 and 2 found morphine-reduction and naloxone-enhancement of defensive sonic vocalizations, as well as other significant or near-significant differences suggesting reduced defensive reactivity to tactile stimuli following morphine administration. It is notable that none of the A/DTB tests or measures involve actual contact with the predator. Thus the present morphine results could be interpreted as involving a high-magnitude morphine reduction in defensive reactivity to tactile stimulation combined with a morphine enhancement of general defensiveness.

It is notable that two previous studies have reported morphine/opiate/opioid enhancement of defense: Puglisi-Allegra et al. (38) found increased conspecific defense to strange intruders in individually housed mice with intraventricular injections of morphine, beta-endorphin, and d-Ala-d-Leu-enkephalin (DADL). Poshivalov (37) reported increased defensive responses toward male intruders by isolated male mice after ICV administration of kyotrophin and neo-endorphin. Since both procedures involved conspecific agonistic interactions among male mice, these findings do not immediately appear to fit the interpretation that morphine-enhanced defensiveness is best seen in the context of threat without tactile contact. In both studies, however, the threat stimuli were male intruders that had just been introduced into the home cage of a resident male, and were very unlikely to have initiated attack against the resident male subjects, suggesting that these tests may have been unusual in producing relatively little tactile contact or pain to the subjects. Thus the finding of morphine-enhanced defensiveness in these two studies, in contrast to social interaction tests in a neutral arena, or with the intruder serving as subject [e.g., (26)] is consonant with an interpretation that morphine may influence defense differentially through mechanisms involving, or not involving, tactile reactivity.

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