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Cocaine Produces Panic-Like Flight Responses in Mice in the Mouse Defense Test Battery

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BLANCHARD, R. J., J. N. KAAWALOA, M. A. HEBERT AND D. C. BLANCHARD. *Cocaine produces panic-like flight responses in mice in the mouse defense test battery.* PHARMACOL BIOCHEM BEHAV **64**(3) 523–528, 1999.— There is an emerging body of clinical evidence that cocaine use in humans can result in serious fear or panic-related emotional disturbances. The present study evaluated the effects of cocaine administration upon defensive responses of mice to a predator (rat) in a Mouse Defense Test Battery (MDTB) that permits the display of the full range of the mouse defensive behaviors: avoidance/escape, flight, freezing, defensive upright, and defensive threat and attack. Mice were tested 30 min following intraperitoneal (IP) injections of either 0, 10, 20, or 30 mg/kg cocaine hydrochloride suspended in physiological saline. Cocaine produced an increase in flight and escape responses throughout the subtests comprising the MDTB. The percentage of subjects exhibiting escape increased in cocaine-treated mice in the Predator Avoidance Test. Cocaine increased mean flight speed and maximum flight speed in the Flight/Chase Test; frequency of flight responses in the Straight Alley Test; and the number of flight attempts in the Forced Contact test. The predominance of flight responding throughout the tests masked any possible cocaine effects on other defenses. The present findings indicate that cocaine may exert its panic-producing effects by acting upon particular neurobehavioral systems subserving defensive behavior. © 1999 Elsevier Science Inc.

Fear Anxiety Panic Defense Drugs of abuse

THERE is increasing evidence that cocaine, despite its reward value, can increase anxiety or panic states in human users (6), and, that these "anxiogenic" effects are manifest during use of the drug, in addition to periods of withdrawal. Case reports (9,10), correlational evidence (3,22), and experiments involving cocaine abusers (19) all suggest that cocaine can, at least in some individuals, elicit or potentiate panic. Although the risk of panic increases with prolonged use or with consumption of high amounts of the drug, panic attacks may also appear after infrequent use of even small amounts of cocaine (10).

Although most studies using animals models to investigate the anxiogenic effects of cocaine have focused on cocaine withdrawal effects (4,15,20,23,24), there is considerable evidence that in these models, as in humans, anxiety-like behaviors can be triggered by cocaine administration. For example, acute cocaine increased thigmotaxis (a defensive behavior) in mice (25) and increased the aversive response to the white area of a black–white test box (5). Both acute and chronic cocaine increased defensive withdrawal in rats (27), and acute cocaine administration increased anxiety-like behavior in mice in the elevated plus-maze (27), an effect observed even at small doses for some subgroups of mice (21). Cocaine was also reported to produce hypervigilance and "panic-like" flight behaviors in monkeys (7).

There have been few attempts to examine cocaine effects on defensive behavior per se, particularly in contexts designed to permit the full expression of the defensive behavior repertory. We have developed a Mouse Defense Test Battery (MDTB) designed to evaluate the spectrum of defensive reactions to a natural predator, the rat. A number of psychoactive drugs have been evaluated in this test (1), and a consistent pattern of results has emerged. Of the range of defensive behaviors, active defenses such as flight and escape appear to be selectively responsive to panicogenic compounds such as yohimbine (3), as well as to chronic administration of panicolytic compounds such as alprazolam (13), imipramine, and fluoxetine (11). In contrast, neither classic benzodiazepines such as diazepam and chlordiazepoxide nor serotonergic anxiolytics (e.g., gepirone) systematically affect these measures (but rather affect other measures) (12,14). The aim of the present study was to examine the effects of cocaine on mouse de-

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fenses in the MDTB. Observation of a selective increase in flight and active defenses would provide further and specific evidence that cocaine produces panic-like effects.

METHOD

Animals

Subjects were 64 naive male Swiss–Webster mice obtained from Charles River Laboratories, 60–75 days old at the beginning of the experiment. They were singly housed in polycarbonate cages in a room maintained under a 12 L:12 D cycle.

Drug and Treatment Groups

Cocaine hydrochloride was dissolved in a vehicle of isotonic saline to various concentrations such that injections were given at a constant volume of 5.0 ml/kg. Mice were randomly assigned to groups of 16, treated with cocaine at doses of 10, 20, or 30 mg/kg or the drug vehicle alone. Injections were administered intraperitoneally (IP) 30 min before the MDTB was administered.

Apparatus

The MDTB was conducted in an oval runway, 0.40 m wide, 0.30 m high, and 4.8 m in total length, consisting of two 2.0-m straight segments joined by two 0.4-m curved segments, and separated by a median wall ($2.0 \times 0.30 \times 0.006$ m). The apparatus was elevated to a height of 0.80 m from the floor to minimize the mouse's visual contact with the experimenter. All parts of the apparatus were made of Plexiglas. The floor of the runway was marked with lines every 20 cm, to facilitate distance measurement. Activity was recorded with video cameras mounted above the apparatus.

Procedure

Pretest. Evaluation of motor responses to drug treatment. Subjects were placed in the runway for a 3-min familiarization period. The number of line crossings, wall rears, wall climbs, and jump escape attempts were recorded (min 1–3).

Reactions to the Predator

Predator avoidance test (min 4–6). Immediately after the familiarization period, a recently killed hand-held (male) rat (*Rattus norvegicus*) was introduced into the runway and brought up to the subject at a speed of approximately 0.5 m/s. Approach was terminated when contact with the subject was made or the subject ran away from the approaching rat. If the subject fled, avoidance distance (the distance from the rat to the subject at the point of flight) was recorded. If the subject did not flee, an avoidance distance of 0.0 m was recorded. The escape distance, the distance that a subject fled, was also recorded. This was repeated five times.

Chase/flight test (min 7–8). The hand-held rat was brought up to the subject at a speed of approximately 2.0 m/s. The time required to chase the subject a distance of 14.4 m (three laps) was recorded. Overall flight speed (m/s) and maximum linear flight speed (an average of three measures of uninterrupted straight flight, over a 1-m linear segment of the runway) were subsequently calculated from these measures. In addition, the number of stops (pause in locomotion), orientations (toward the oncoming rat after coming to a stop), jump attacks, jump escapes, wall climbs, and reversals (subject turned and ran in the opposite direction) were recorded.

Straight alley (min 9–11). The runway was then converted to a straight alley by the closing of doors at both ends. The hand-held rat was moved to a distance of 0.80, 0.60, and 0.20 m from the subject and held at each location for 15 s. Measures taken included immobility (freezing) time, approaches/withdrawals, closest distance between the subject and the rat, flight, wall climbs, jump escapes and jump attacks, contacts with the rat, total contact duration, and the time out of the first square.

Forced contact (min 12). The experimenter brought the (nose of the) rat up to contact the head of the subject three times with 5 s between contacts. For each such contact, bites, vocalizations, upright postures, jump attacks, and jump escapes (differentiated by orientation with respect to the predator) by the subjects were measured.

Statistics

One-way between-subjects ANOVAs were performed for each behavioral measure. Alpha was set at 0.05. Post hoc analyses of specific group differences were carried out with the Newman–Keuls test (alpha = 0.05).

RESULTS

Pretest (Motor Responses)

Cocaine had no effect upon locomotor activity in the 3-min pretest (see Table 1). ANOVA revealed no effect of dose on number of line crossings, $F(3, 60) = 0.97$, $p = 0.41$, wall rears, $F(3, 60) = 0.86$, $p = 0.47$, wall climbs, $F(3, 60) = 0.81$, $p = 0.50$, or jump escapes, $F(3, 60) = 0.67$, $p = 0.58$.

Reactions to the Predator

Predator avoidance test. There was no effect of cocaine on the percentage of subjects that exhibited avoidance in the approach test, $F(3, 60) = 1.93$, $p = 0.13$, nor was there an effect of dose on mean avoidance distance, $F(3, 60) = 0.84$, $p = 0.48$. There was, however, a significant effect of cocaine dose on the

TABLE 1

LOCOMOTOR BEHAVIOR IN PRETEST PERIOD PRIOR TO PREDATOR EXPOSURE

	0 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg
Lines crossed	174.25 ± 19.14	180.94 ± 16.22	208.00 ± 10.77	193.51 ± 12.99
Wall rear	3.44 ± 0.47	5.13 ± 1.02	4.81 ± 0.82	4.25 ± 0.78
Wall climb	1.31 ± 0.33	1.75 ± 0.61	2.44 ± 0.63	1.63 ± 0.48
Jump Escape	0.00 ± 0.00	0.06 ± 0.06	0.06 ± 0.06	0.00 ± 0.00

Data are presented as means ± SEM.

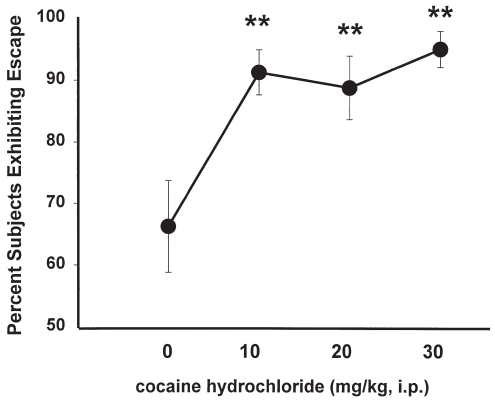

FIG. 1. Percentage of subjects that exhibited escape as a function of cocaine dose in the Predator Avoidance Test. $^{**}p < 0.01$.

percentage of mice that displayed escape when contacted, $F(3, 60) = 6.47$, $p < 0.001$. Subsequent Newman–Keuls tests showed a significant increase at the 10, 20, and 30 mg/kg doses ($p < 0.01$) in percent escape compared to saline controls (see Fig. 1). There was a nearly significant (increasing) effect of cocaine dose on mean escape distance, $F(3, 60) = 2.63$, $p = 0.06$.

Chase/flight test. Figure 2a presents the mean overall flight speed as a function of cocaine dose in the chase/flight test. ANOVA revealed a significant increasing effect of dose on mean flight speed, $F(3, 58) = 6.31$, $p < 0.001$. Subsequent Newman–Keuls tests revealed significant increases for this measure at 10 mg/kg ($p < 0.01$), 20 mg/kg ($p < 0.01$), and 30 mg/kg ($p < 0.001$) compared to the saline. Figure 2b shows the mean maximum linear flight speed as a function of cocaine dose. An ANOVA revealed a significant increasing effect of dose for this measure as well, $F(3, 57) = 2.95$, $p < 0.05$. The Newman–Keuls indicated a reliable difference between the 30 mg/kg and saline group only ($p < 0.05$). Results of the other behavioral measures taken during this test (stops, reversals, orientations, jump escapes, jump attacks, wall climbs) are presented in Table 2. Of these measures, cocaine affected only the number of stops, $F(3, 58) = 3.10$, $p < 0.05$. A Newman–Keuls test indicated a significant reduction in stops compared to the saline group at the 10 and 30 mg/kg doses ($p < 0.05$).

Straight alley. Behaviors measured in this test are summarized in Table 3. ANOVA revealed a reliable effect of cocaine dose on flight, $F(3, 60) = 5.35$, $p < 0.005$, with increases in flight at the 10 mg/kg ($p < 0.05$), 20 mg/kg ($p < 0.05$), and 30 mg/kg ($p < 0.01$) doses compared to saline. Dose effects

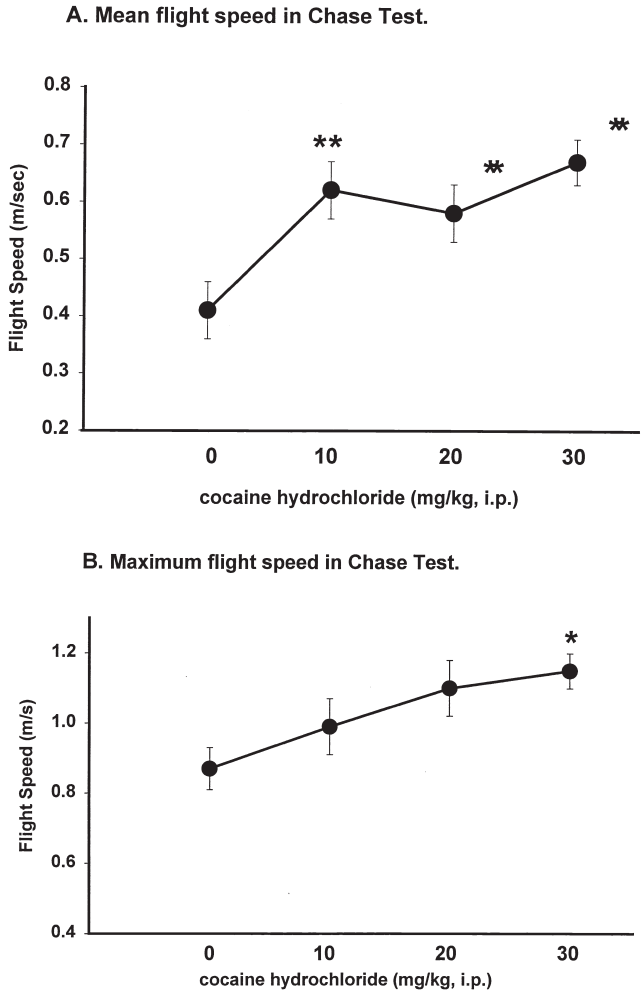

FIG. 2. (A) Indicates mean flight speed in the Chase Test as a function of cocaine dose. $^{**}p < 0.01$. (B) Illustrates maximum flight speed in the Chase Test as a function of cocaine dose. $^{*}p < 0.05$.

were reliable for frequency of jump escapes, $F(3, 60) = 3.60$, $p < 0.05$, with higher numbers exhibited at the 10 and 20 mg/kg dose compared to saline ($p < 0.05$), and immobility, $F(3, 60) = 3.04$, $p < 0.05$; 30 mg/kg < saline, $p < 0.05$. It is particularly notable that risk assessment behaviors like approaches/withdrawals re the threat stimulus; closest distance between ani-

TABLE 2
FREQUENCIES OF BEHAVIORS IN CHASE/FLIGHT TEST

	0 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg
Stops	9.40 ± 1.05	6.07 ± 0.73*	7.50 ± 1.01	6.06 ± 0.72*
Reversals	1.73 ± 0.64	2.00 ± 0.55	2.63 ± 0.62	2.94 ± 0.60
Orientations	4.53 ± 1.11	2.07 ± 0.44	3.75 ± 0.69	2.56 ± 0.65
Jump escapes	0.40 ± 0.21	0.93 ± 0.51	1.13 ± 0.35	0.88 ± 0.29
Jump attacks	0.33 ± 0.19	0.20 ± 0.11	1.00 ± 0.34	0.63 ± 0.27
Wall climbs	0.00 ± 0.00	0.00 ± 0.00	0.13 ± 0.13	0.06 ± 0.06

Data are presented as means ± SEM.
$^{*}p < 0.05$.

TABLE 3
BEHAVIORAL RESPONSES IN THE STRAIGHT ALLEY TEST

	0 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg
Approach/withdrawal	3.88 ± 0.48	4.44 ± 0.44	5.56 ± 0.71	5.44 ± 0.56
Flight	0.50 ± 0.22	1.88 ± 0.41*	2.25 ± 0.43*	2.81 ± 0.56*
Jump escape	0.31 ± 0.15	3.06 ± 1.04*	3.44 ± 0.96*	1.88 ± 0.42
Jump attack	0.00 ± 0.00	0.13 ± 0.09	0.13 ± 0.09	0.19 ± 0.10
Wall climb	2.75 ± 0.66	3.63 ± 0.66	3.13 ± 0.68	3.38 ± 0.76
Immobility(s)	8.46 ± 1.80	5.50 ± 1.26	3.98 ± 1.29	2.96 ± 1.02*
CDBA	36.9 ± 14.4	31.6 ± 9.81	10.9 ± 4.09	28.1 ± 10.4
OFS(s)	29.8 ± 3.45	25.8 ± 2.30	29.9 ± 1.93	28.4 ± 1.89
Contact	3.50 ± 0.72	3.31 ± 0.51	4.31 ± 0.78	4.44 ± 0.72
Contact duration(s)	14.6 ± 2.87	7.01 ± 2.01	7.41 ± 2.28	7.40 ± 1.83

Data are presented as means ± SEM.
*$p < 0.05$.

mals (CDBA); and time out of first square (OFS) showed no systematic change with cocaine.

Forced contact. Figure 3 shows the mean frequency of behavioral responses to forced contact across cocaine doses. ANOVA revealed a significant increasing effect of cocaine dose on the number of flight attempts, $F(3, 60) = 12.59$, $p < 0.00001$. Subsequent Newman–Keuls tests showed an increase in this measure at each of the doses compared to saline ($p < 0.001$). Cocaine had no significant effects on any of the other behavioral measures.

DISCUSSION

The main finding was an overall increase in flight and escape responses throughout the subtests comprising the MDTB. In the predator avoidance test, although avoidance distances were not increased, both the percentage of subjects that exhibited an escape response and escape distance were increased with cocaine administration. Flight was by far the predominant response in the chase/flight test with mean flight speed increased at all cocaine doses, although maximum speed increased only at the highest dose. Flight remained high even in the straight alley test, in which the stimulus animal remained at fixed distances from the subject (did not approach the subject). Finally, in the forced-contact test, the most prevalent response again was flight rather than other defenses such as upright defense posture and biting, typical responses of (laboratory) mice at close distances.

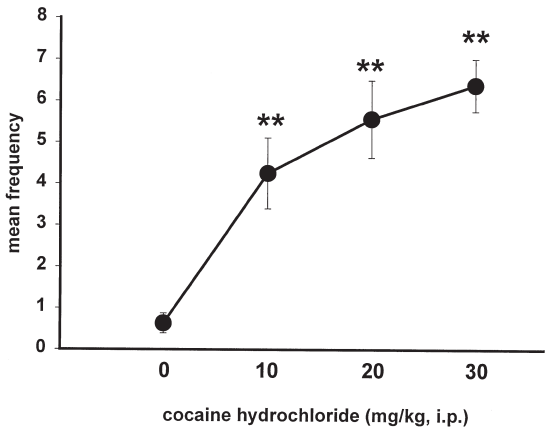

FIG. 3. Mean number of flight attempts in the Forced Contact Test as a function of cocaine dose. **$p < 0.01$.

In the pretest, prior to exposure to the threat stimulus, cocaine did not significantly increase any of the motoric measures, including the number of lines crossed. This somewhat surprising lack of a cocaine effect on locomotion, even for high-dose animals, may have been due to either the relatively long injection-test interval (30 min), to a novelty-stress enhancement of locomotion for the saline control group, or to both. However, because the predator tests immediately followed this pretest activity measure, neither time nor novelty factors can be considered to have changed substantially between the two. Thus, the increase in flight to the predator for cocaine-treated mice appears to be related to increases in defensiveness per se, rather than a generalized increase in motor behavior. The difference between pretest and test behavior is also important, because it suggests that cocaine does not induce flight in the absence of the stimuli that normally produce it, but that instead, cocaine potentiates the flight that is induced by appropriate threat stimuli.

The pattern of defensive behavior exhibited by cocaine-treated mice in the present study resembled that of wild mice. Compared to laboratory (Swiss) mice, a wild-derived strain (fourth generation) of mice from Italy exhibited high levels of flight and escape in the MDTB, and a reduction in other defenses such as upright defense and biting (2). The reduction in other defenses in wild mice was thought to reflect a masking effect of active defense; that is, the wild mouse tended to flee well before the predator was close enough to permit the display of other defensive behaviors that require close proximity. When tested in a small compartment that precluded flight, wild mice did exhibit upright defenses and biting. Similarly, cocaine-treated animals may not have exhibited other defenses because flight was an available (albeit sometimes difficult) defensive option in all subtests of the present study. We have recently examined the effects of high doses of intravenously administered cocaine on defensive reactions of laboratory rats to a conspecific in a similar test situation (16). Whereas controls failed to show flight and other defenses, rats administered cocaine exhibited potent flight and escape responses, and when flight was prevented, they adopted an upright defense posture and exhibited defensive biting. Thus, it would be interesting to examine cocaine-treated mice in a test environment even more restrictive than that used in the forced-contact test of the present study to determine whether

cocaine affected flight systems alone or increased defenses in general.

The rat data (16) are interesting also because these animals were tested either (Experiment 1) immediately after IV cocaine administration, or (Experiment 2) at injection-test intervals of 0, 5, 15, and 30 min. The flight results of those tests provide a clear parallel to those obtained in the present tests, and reliable increases were found at all four of these injection-test intervals. However, flight speeds in the chase test at the longer injection-test intervals (15 and 30 min) were reliably less than for the shorter injection-test intervals, albeit still significantly higher than for the corresponding saline tests. Thus the present procedure, utilizing a relatively long (30 min) IP injection-test interval, may be providing a rather conservative estimation of the potentiation of flight by IP cocaine, suggesting a need for parametric evaluation of injection-test intervals, as well as a need to evaluate lower cocaine doses (as all present doses produced strong, perhaps asymptotic, effects on some flight measures), in this procedure. However, the rat data (Experiment 2), showing this decline in flight effects over 30 min after injection, do suggest that a 30-min injection-test interval for IV cocaine measures the effect of cocaine on flight, as opposed to withdrawal effects that might emerge as brain drug levels decline.

In previous MDTB studies, the panicogenic compound yohimbine produced similar increases in flight and escape responses without affecting other defensive behaviors (3), suggesting flight and active defenses in this test may selectively model panic, whereas some other defensive responses may reflect anxiety (1). This idea was supported by additional MDTB studies of clinically effective antipanic agents such as alprazolam (13), fluoxetine, and imipramine (11), which suppressed flight in this test when given on a chronic, but not an acute, basis. Thus, the selective increase of flight in the present study suggests a strong panicogenic profile for cocaine in mice manifested throughout the MDTB tests, even those in which flight is not the dominant response. Because flight was so predominant after cocaine administration, these tests may not be definitive for other defensive behaviors, some of which might show increases with cocaine in situations in which flight is not possible.

These findings support clinical reports of panic with cocaine use and add to a growing list of animal studies, suggesting a panicogenic dimension to cocaine. Some of these studies indicate that the defense effects of cocaine may be present at dose levels that also induce reward effects. All three of the doses giving reliable flight effects in the present study (10, 20, and 30 mg/kg of cocaine) have been used sucessfully to induce conditioned place preferences in mice (18,26). In rats, studies by Ettenberg and Geist, (8) and Heinrichs et al. (17) have demonstrated intravenous (IV) self-administration of cocaine at doses (0.75 mg/kg $\times$ 4 in a 2-min period) that are comparable to the IV doses that (16) produced explosive flight reactions. In the Ettenberg and Geist (8) and Heinrichs et al. (17) studies, cocaine produced an approach–avoidance conflict with reference to criterion behaviors, manifested by repeated approaches to and withdrawals from the area in which cocaine was given. These findings provide a very clear indication that one and the same dose of cocaine may have both rewarding and aversive effects, and suggest that aversive, defense-inducing effects of cocaine may be a common concomitant of the subjective experience of cocaine. If this view is correct, then interoceptive, defense-related effects of cocaine would be expected to constitute a potentially important component of the subjective stimuli associated with cocaine use, and to interact with the additional effects of the drug in terms of conditioning, habituation, and sensitization. Thus, in addition to clarification of cocaine-associated panic and anxiety effects, characterization of cocaine's effects on defense systems may be crucial for an understanding of conditioning and related phenomena associated with cocaine use and withdrawal.

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REFERENCES

1. Blanchard, R. J.; Griebel, G.; Henrie, J. A.; Blanchard, D. C.: Differentiation of anxiolytic and panicolytic drugs by effects on rat and mouse defense test batteries. Neurosci. Biobehav. Rev. 21:783–789; 1997.
2. Blanchard, R. J.; Hebert, M. A.; Palanza, P.; Figueira, R.; Blanchard, D. C.; Parmigiani, S.: Defensive behaviors in wild and laboratory (Swiss) mice: The mouse defense test battery. Physiol. Behav. 65:201–209; 1998.
3. Blanchard, R. J.; Taukulus, H. K.; Rodgers, R. J.; Magee, L. K.; Blanchard, D. C.: Yohimbine potentiates active defensive responses to threatening stimuli in Swiss–Webster mice. Pharmacol. Biochem. Behav. 44:673–681; 1993.
4. Costall, B.; Jones, B. J.; Kelly, M. E.; Naylor, R. J.; Onaivi, E. S.; Tyers, M. B.: Ondansetron inhibits a behavioural consequence of withdrawing from drugs of abuse. Pharmacol. Biochem. Behav. 36:339–344; 1990.
5. Costall, B.; Kelly, M. E.; Naylor, R. J.; Onaivi, E. S.: The actions of nicotine and cocaine in a mouse model of anxiety. Pharmacol. Biochem. Behav. 33:197–203; 1989.
6. Cox, B. J.; Norton, G. R.; Swinson, R. P.; Endler, N. S.: Substance abuse and panic-related anxiety: A critical review. Behav. Res. Ther. 28:385–393; 1990.
7. Crowley, T. J.; Mikulich, S. K.; Williams, E. A.; Zerbe, G. O.; Ingersoll, N. C.: Cocaine, social behavior, and alcohol-solution drinking in monkeys. Drug Alcohol Depend. 29:205–223; 1992.
8. Ettenberg, A.; Geist, T. D.: Animals model for investigating the anxiogenic effects of self-administered cocaine. Psychopharmacology (Berlin) 103:455–461; 1991.
9. George, M. S.; Ballenger, J. C.: The neuroanatomy of panic disorder: The emerging role of right parahippocampal region. J. Anxiety Disord. 6:181–188; 1992.
10. Geracioti, T. D.; Post, R. M.: Onset of panic disorder associated with rare use of cocaine. Biol. Psychiatry 29:403–406; 1991.
11. Griebel, G.; Blanchard, D.C.; Agnes, R.; Blanchard, R. J.: Differential modulation of antipredator defensive behavior in Swiss–Webster mice following acute and chronic treatment with imipramine and fluoxetine. Psychopharmacology (Berlin) 120:57–66; 1995.
12. Griebel, G.; Blanchard, D. C.; Jung, A.; Blanchard, R. J.: A model of "antipredator" defense in Swiss–Webster mice: Effects of benzodiazepine receptor ligands with different intrinsic activities. Behav. Pharmacol. 6:732–745; 1995.
13. Griebel, G.; Blanchard, D. C.; Jung, A.; Lee, J.; Masuda, C. K.; Blanchard, R. J.: Further evidence that the Mouse defense Test Battery is useful for screening anxiolytic and panicolytic drugs: Effects of acute and chronic treatment with alprazolam. Neuropharmacology 34:1625–1633; 1995.
14. Griebel, G.; Blanchard, D. C.; Jung, A.; Masuda, C. K.; Blanchard, R. J.: 5-HT_{1A} agonists modulate mouse antipredator defensive behavior differently than the preferential 5-HT_{2A}

receptor antagonist pirenperone. Pharmacol. Biochem. Behav. 51:235–244; 1995.
15. Harris, G. C.; Aston-Jones, G.: β-Adrenergic antagonists attenuate withdrawal anxiety in cocaine- and morphine-dependent rats. Psychopharmacology (Berlin) 113:131–136; 1993.
16. Hebert, M. A.; Wiggen, J. D.; Blanchard, D. C.; Blanchard, R. J.: Intravenous cocaine precipitates panic-like flight responses and lasting hyperdefensiveness in laboratory rats. Pharmacol. Biochem. Behav. (in press).
17. Heinrichs, S. C.; Klaassen, A.; Koob, G. F.; Schulteis, G.; Ahmed, S.; De Souza, E. B.: Corticotropin-releasing factor receptor blockade enhances conditioned aversive properties of cocaine in rats. Psychopharmacology (Berlin) 136:247–255; 1998.
18. Kamei, J.; Ohsawa, M.: Effects of streptozotocin-induced diabetes on place conditioning action of cocaine in mice. Jpn. J. Pharmacol. 75:299–301; 1997.
19. McDougle, C. J.; Black, J. E.; Malison, R. T.; Zimmerman, R. C.; Kosten T. R.; Heninger G. R.; Price L. H.: Noradrenergic dysregulation during discontinuation of cocaine use in addicts. Arch. Gen. Psychiatry 51:713–719; 1994.
20. Meert, T. F.: Ritanserin overcomes exploratory inhibition induced by cocaine withdrawal. Behav. Pharmacol. 3:149–154; 1992.
21. Rogerio, R.; Takahashi, R. N.: Anxiogenic action of acute but not repeated cocaine administration in handling-habituated mice in the pluz-maze test. Braz. J. Med. Biol. Res. 25:713–716; 1992.
22. Rosen, M. I.; Kosten, T. R.: Cocaine-associated panic attacks in methadone-maintained patients. Am. J. Drug Alcohol Abuse 18:57–62; 1992.
23. Prather, P. L.; Lal, H.: Protracted withdrawal: Sensitization of the anxiogenic response to cocaine in rats concurrently treated with ethanol. Neuropsychoparmacology 6:23–29; 1992.
24. Sarnyai, Z.; Biro, E.; Gardi, J.; Vecsernyes, M.: Brain corticotropin-releasing factor (CRF) in the mediation of the behavior induced by cocaine withdrawal in rats. Brain Res. 675:89–97; 1995.
25. Simon, P.; Dupuis, R.; Costentin, J.: Thigmotaxis as an index of anxiety in mice: Influence of dopaminergic transmission. Behav. Brain Res. 61:59–64; 1994.
26. Tokuyama, S.; Takahashi, M.; Kaneto, H.: The effect of ginseng extract on locomotor sensitization and conditioned place preference induced by methamphetamine and cocaine in mice. Pharmacol. Biochem. Behav. 54:671–676; 1996.
27. Yang, X. M.; Gorman, A. L.; Dunn, A. J.; Goeders, N. E.: Anxiogenic effects of acute and chronic cocaine administration: Neurochemical and behavioral studies. Pharmcaol. Biochem. Behav. 41:643–650; 1992.