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The Mouse Defense Test Battery: An Experimental Model of Different Emotional States

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There are few well-accepted animal models of psychiatric disorders. However, a number of animal models of anxiety have been proposed, most of which involve exposure of animals to external (e.g., cues previously paired with footshock) or internal (e.g., drugs) stimuli that are assumed to be capable of inducing anxiety in humans. The actual measures taken include suppression of previously punished activities, conditioned emotional responses, a range of sonic and ultrasonic vocalizations, and social and exploratory behaviors (for reviews, see Sanger, Perrault, Morel, Joly, & Zivkovic, 1991; Treit, 1985).

The suggestion has been made many times that defensive behaviors of lower mammals constitute a significant model for understanding human emotional disorders (e.g., R. J. Blanchard & Blanchard, 1984; see also Brain & Marrow, this volume). Defensive behaviors occur in response to a number of threatening stimuli, including predators, attacking conspecifics, and dangerous objects or situations. Such behaviors can readily be studied in wild rats, which show a complete defensive repertoire in response to danger. In contrast, in laboratory rats, defensive threat and attack behaviors in response to predators have been much reduced through systematic selection for docility by breeders (R. J. Blanchard, Flannelly, & Blanchard, 1986). However, the disadvantages of using wild rats as subjects in laboratory research are obvious. For example, it is clear that the difficulty and cost in obtaining and maintaining these animals are greater than for laboratory rats.

There are reasons to believe that the laboratory mouse has not been so severely selected on the basis of its defensive behaviors. The smaller size of the mouse and its reduced potential to inflict serious wounds, plus the ease of handling mice with a tail pickup, have enabled greater tolerance of defensive attack behavior in this species, and indeed, domesticated

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mice often show biting behavior to human handling (R. J. Blanchard, Parmigiani, Agullana, Weiss, & Blanchard, 1995). Thus, it has been demonstrated that mice from four lines—three inbred (BALB/c, C57BL/6, and DBA/2) and one outbred (Swiss)—show intense defense reactions when confronted with an approaching threat stimulus (laboratory rat). They display initial flight, followed by risk assessment (RA), and defense vocalization and biting occur when escape is blocked (Griebel, Sanger, & Perrault, 1997). The concept of RA has emerged from the work of D. C. Blanchard, Blanchard, and Rodgers (1991). These authors have defined RA in terms of orientation toward present or potential threat, often followed by specific approach responses. D. C. Blanchard et al. have demonstrated that RA is associated with gathering of information concerning threat sources. Together, these defense patterns closely resemble those of wild rats, suggesting that mice of these strains do not show the reductions in flight and defensive threat–attack that are typical of laboratory rats. Such findings clearly indicate that the laboratory mouse may be a suitable subject for studies concerned with defensive behaviors.

However, it was not clear in these initial studies whether the responses displayed by the mice were specific to the encounter with a laboratory rat. The idea that defensive reactions might be elicited by any approaching stimulus was addressed by studying the influence of various stimuli on defensive reactions of Swiss mice (Griebel, Blanchard, Jung, & Blanchard, 1995). Briefly, this study demonstrated that when compared with mice approached by a leather glove, mice confronted with an anesthetized or conscious rat displayed potentiated flight responses and defensive threat–attack reactions, whereas RA behavior was generally similar in all three conditions. Furthermore, escape attempts after removal of the stimulus were higher in the rat conditions compared with the leather glove group. In this latter case, however, responses displayed by the leather glove group mice were also higher than those observed in a group that was not exposed to any stimulus, indicating that the leather glove stimulation also elicited defense reactions, albeit at a lower level. Together, these results demonstrate that a rat stimulus elicits higher levels of flight reactions and defensive threat–attack responses than a leather glove stimulus, thereby suggesting that this experimental situation is appropriate for investigating antipredator defense. The aim of the present chapter is to provide evidence that antipredator defense behaviors elicited in mice by the encounter with a rat may be useful to model different aspects of human anxiety.

The Mouse Defense Test Battery

The Mouse Defense Test Battery (MDTB) consists of an oval runway based on that used in the Fear Defense Test Battery with rats (for more details, see R. J. Blanchard, Blanchard, Rodgers, & Weiss, 1990; Griebel, Blanchard, Jung, & Blanchard, 1995). However, specific situational and behavioral components of the Anxiety Defense Test Battery (R. J.

Table 6.1. Defensive Behaviors Elicited in the Mouse by the Exposure to a Rat and the Corresponding Parameters Recorded in the Mouse Defense Test Battery

Defensive behavior	Parameters
Risk assessment	Stops and orientations when the mouse is chased by a rat; approaches followed by withdrawal responses toward the rat, which remains at a constant distance (the mouse is trapped in one part of the runway)
Flight	Avoidance distance and frequency of avoidance when the rat is introduced into the runway apparatus
Defensive threat–attack	Vocalizations, biting, and upright postures on forced contact with the rat
Contextual defense	Escape attempts from the runway after the rat has been removed from the test area

Blanchard et al., 1990), involving reactivity to stimuli associated with potential threat rather than to the actual presence of an approaching predator, are incorporated into the MDTB. Briefly, the MDTB consists of five tests associated either with potential threat (contextual defense) or with the actual presence of an approaching threat (i.e., a rat). The latter focuses on changes in flight, RA, and defensive threat–attack behaviors, whereas the former involves escape attempt responses from the runway cage (see Table 1).

In the contextual defense situation, postpredator escape attempts from the runway cage are dramatically increased when compared with the performance measured before the confrontation with the rat. Similarly, in response to an approaching predator, mice invariably show active flight behavior, and when subjects run to escape the chasing predator, they frequently show RA consisting of an abrupt movement arrest often followed by orientation to the oncoming predator. Furthermore, when mice are constrained in one part of the runway, they often display active RA, consisting of approaches to the predator followed by withdrawals. Finally, defensive threat and attack to the rat occur almost invariably on forced contact (Griebel, Blanchard, Jung, & Blanchard, 1995). This pattern of responding can be quantified using the specific behavioral parameters listed in Table 1.

Evidence That Defense Reactions Relate to Different Emotional States

It has been suggested that defense responses of rats confronted with a predatory stimulus provide an appropriate laboratory model for investigating behavior relevant to human emotional disorders (R. J. Blanchard & Blanchard, 1984). Subsequent investigations with anxiolytic compounds have confirmed this idea (for review, see R. J. Blanchard, Yudko, Rodgers, & Blanchard, 1993). Interestingly, these studies indicated that

defense reactions may be used to differentiate between several classes of anxiolytic drugs. For instance, benzodiazepines (BZPs; e.g., diazepam or chlordiazepoxide), serotonin receptor ligands (e.g., buspirone, gepirone, or 8-hydroxy-2-(di-n-propylamino)-tetralin [8-OH-DPAT]), and alcohol produce modification in responding primarily involving RA and defensive threat–attack reactions. Interestingly, these latter responses showed a bidirectional (increase at low doses and decrease at high doses) response to alcohol, indicating some differences between alcohol and BZPs, suggesting that particular patterns of drug effects may map rather precisely onto the target symptoms for specific psychopathologies. Therefore, the relationships between the variety of responses measured in the MDTB become an important issue. Do these different responses provide different measures of the same state, or do they measure distinct states of defensiveness, fear, or anxiety? This question can be approached by (a) performing a factor analysis of the various behavioral defense reactions observed in the battery and (b) comparing the effects of drugs used in the clinical management of different anxiety disorders (i.e., generalized anxiety disorder [GAD] and panic disorder [PD]).

Evidence From Factor Analysis

Factor analyses are commonly used to describe the relationships among different variables and, consequently, to identify specific indexes or factors, such as Anxiety or Locomotor Activity. Performed on the behaviors recorded in the MDTB, this analysis identified three main independent factors (Griebel, Blanchard, & Blanchard, 1996; see Exhibit 1). Factor 1 included cognitive aspects of defensive behaviors that appear to be related to the process of acquiring and analyzing information in the presence of threatening stimuli (i.e., RA). Flight responses loaded heavily on Factor 2 and to a lesser extent on Factor 3. Several defensive threat–attack reactions (i.e., upright postures and biting) and escape attempts loaded highly on Factor 3, indicating that this factor reflects more affective defense reactions. Together, this pattern is consistent with the idea that defense reactions of mice exposed to a threat stimulus relate to different emotional states.

Exhibit 6.1. Main Factor Loadings of the Various Defensive Behaviors in the Mouse Defense Test Battery

Factor 1	Factor 2	Factor 3
Stops	Avoidance distance	Biting
Orientations	Avoidance frequency	Upright postures
Approaches followed by withdrawal responses		Avoidance distance
		Escape attempts

Evidence From Drug Effects

The clinical evidence for a dissociation of GAD and PD, on the basis of drug response, is controversial (Lister, 1991). However, there is general agreement that a range of tricyclic antidepressants, serotonin reuptake inhibitors (SSRIs), inhibitors of monoamine oxidase (MAO inhibitors), the triazolobenzodiazepine alprazolam, and some other high-potency BZPs (e.g., clonazepam) are effective against PD (Burrows, Judd, & Norman, 1993; Priest, Gimbrett, Roberts, & Steinert, 1995). In addition, clinical and basic studies support the involvement of cholecystokinin (CCK) in PD (Bradwejn, Koszycki, Couetoux du Tertre, & Bourin, 1992; Van Megen, Den Boer, & Westenberg, 1994). By contrast, drugs used against GAD, such as the traditional BZP receptor full agonists (e.g., chlordiazepoxide or diazepam) and the serotonin receptor agonist buspirone, are of minimal utility in the treatment of PD (Johnson, Lydiard, & Ballenger, 1995; Klein, 1995; Lader, 1994; Roy Byrne, Wingerson, Cowley, & Dager, 1993).

On the basis of these clinical findings, the drugs investigated in the MDTB were divided into three categories (see Table 2): (a) those used against GAD, including two classical BZPs (chlordiazepoxide and diazepam) and one serotonin receptor agonist (gepirone); (b) those effective or potentially effective against PD, including a tricyclic antidepressant (imipramine), an SSRI (fluoxetine), two reversible MAO inhibitors (moclobemide and befloxatone), and two CCK_B receptor antagonists (PD 135,158 and LY 288513); and (c) those used in the treatment of both GAD and PD, represented by the second-generation BZPs alprazolam and clonazepam.

Effects of compounds used in the treatment of GAD. Results indicated that chlordiazepoxide and diazepam reduced RA activities observed in the

Table 6.2. Drugs Tested in the Mouse Defense Test Battery and Their Clinical Efficacy (if Known) in the Management of Generalized Anxiety Disorder (GAD) and Panic Disorder (PD)

Drug	Action–class	GAD	PD
Alprazolam	Benzodiazepine	+	+
Befloxatone	MAOP-A inhibitor		
Chlordiazepoxide	Benzodiazepine	+	(+)
Clonazepam	Benzodiazepine	+	+
Diazepam	Benzodiazepine	+	(+)
Fluoxetine	Serotonin reuptake inhibitor	−	+
Gepirone	Serotonin agonist	+	−
Imipramine	NA/5-HT reuptake inhibitor	−	+
LY 288513	CCK_B antagonist		
Moclobemide	MAO-A inhibitor		+
PD 135, 158	CCK_B antagonist		

Note. MAO = monoamine oxidase; NA/5-HT = noradrenalin/serotonin; CCK = cholecystokinin; + = demonstrated clinical effects; (+) = effective at high and mostly sedative doses; − = negative or inconclusive effects.

Table 6.3. Effects of Various Drugs Effective Against Generalized Anxiety Disorders on Defensive Behaviors in the Mouse Defense Test Battery

	Risk assessment				
Drug	Chase	Straight alley	Flight	Defensive threat and attack	Escape attempts
Chlordiazepoxide	↓	–	(↓)	↓	↓
Diazepam	↓	↑	–	↓	↓
Gepirone	–	–	–	↓	↓

Note. ↓ = a decrease in the response; (↓) = a decrease in the response at motor-impairing doses only; – = ineffective; ↑ = an increase in the response.

chase–flight test, defensive threat–attack reactions induced by physical contact with the rat, and escape attempts after the rat had been removed from the test area (see Table 3). Furthermore, diazepam, but not chlordiazepoxide, slightly increased RA responses displayed when subjects were constrained in one part of the runway. In addition, diazepam failed to affect flight whereas chlordiazepoxide reduced this behavior, albeit at a motor-impairing dose (25 mg/kg; spontaneous locomotor activity was measured in the runway apparatus during a 3-min period preceding the exposure to the rat; Griebel, Blanchard, Jung, & Blanchard, 1995; Griebel, Sanger, & Perrault, 1997). Compared with the BZPs, the serotonin receptor agonist gepirone presented a very similar profile on defensive threat–attack responses, escape attempts, and flight. The former responses were reduced, whereas flight behavior remained unchanged. By contrast, gepirone did not decrease the high level of RA responses when subjects were chased by the rat and did not increase these activities in the straight alley situation (Griebel, Blanchard, Jung, Masuda, & Blanchard, 1995). Together, these results indicate that defensive threat–attack reactions and escape attempts show a consistent response to drugs used in the treatment of GAD regardless of their pharmacological properties. By contrast, RA responses appear to be mainly modulated by BZPs.

Effects of compounds used in the treatment of PD. Imipramine, fluoxetine, and the reversible MAO inhibitors were administered both acutely and chronically because clinical data indicate that long-term treatment is necessary to achieve therapeutic response. The effects of two potential antipanic compounds, PD 135,158 and LY 288513, were investigated after acute treatment.

After single administrations, imipramine, fluoxetine, and both reversible MAO inhibitors did not affect any of the defense responses (see Table 4). Instead, imipramine and fluoxetine potentiated flight responses and defensive biting (data not shown). In sharp contrast with this profile, chronic administration of the two drugs decreased both measures. In addition, imipramine and fluoxetine also decreased RA activities when sub-

Table 6.4. Effects of Various Drugs Effective or Potentially Effective Against Panic Disorder on Defensive Behaviors in the Mouse Defense Test Battery

	Risk assessment				
Drugs	Chase	Straight alley	Flight	Defensive threat and attack	Escape attempts
Befloxatone	–	↑	↓	–	–
Fluoxetine	↓	–	↓	↓	↓
Imipramine	↓	–	↓	↓	↓
LY 288513	–	–	↓	–	–
Moclobemide	–	–	↓	–	–
PD 135,158	–	–	↓	–	–

Note. – = ineffective; ↑ = an increase in the response; ↓ = a decrease in the response. Results refer to effects observed after repeated administration of imipramine, fluoxetine, befloxatone, and moclobemide and acute administration of LY 288513 and PD 135,138.

jects were chased by the rat and escape attempts after the removal of the rat (Griebel, Blanchard, Agnes, & Blanchard, 1995). After repeated administration of the two reversible MAO inhibitors moclobemide and befloxatone, a significant reduction in flight was observed. In addition, befloxatone but not moclobemide increased RA responses when mice were constrained in one part of the apparatus facing the rat, which remained at a constant distance (Griebel, Perrault, & Sanger, 1997). Finally, a single administration of PD 135,158 and LY 288513 resulted in a reduction in the flight measure. No other drug effects were observed with these compounds.

Overall, these results showed that antipanic compounds mainly affected flight reactions. Furthermore, some of these compounds (i.e. imipramine, fluoxetine, and befloxatone) partially affected defensive threat–attack responses and RA activities. In addition, the finding of a potentiation in some defense reactions (i.e., flight and bitings) after a single dose of imipramine and fluoxetine fits well with the clinical observation of an exacerbation in anxious responses that may sometimes occur at the beginning of treatment with imipramine or with an SSRI (Westenberg, 1996; Westenberg & Den Boer, 1993).

Effects of compounds used in the treatment of GAD and PD. Alprazolam and clonazepam displayed very similar behavioral profiles in the MDTB (Griebel, Blanchard, Jung, Lee, et al., 1995; Griebel, Sanger, & Perrault, 1996; see Table 5). The drugs reduced flight, defensive threat–attack reactions, and RA activities during the chase–flight test. In addition, they increased RA in the straight alley situation, although the effect of alprazolam was not statistically significant. Thus, these drugs affected a wider range of defense reactions than compounds used against either GAD or PD.

Table 6.5. Effects of Drugs Effective Against Generalized Anxiety and Panic Disorders on Defensive Behaviors in the Mouse Defense Test Battery

	Risk assessment				
Drugs	Chase	Straight alley	Flight	Defensive threat and attack	Escape attempts
Alprazolam	↓	↑	↓	↓	↓
Clonazepam	↓	↑	↓	↓	↓

Note. ↓ = a decrease in the response; ↑ = an increase in the response.

Discussion

The MDTB: Advantages in Using a Multiparameter Test Paradigm

A major concern with traditional animal models of anxiety is that they are in most cases unable to discriminate between anxiolyticlike effects induced by BZPs, serotonin receptor agonists, or SSRIs, although clinical findings strongly indicate differential therapeutic efficacy of these agents, according to the anxiety disorder treated. On the basis of these observations, it is clear that the major advantage of the MDTB is that it provides multiple measures that may be differentially involved in various forms of anxiety. The factor analysis performed on the different defense reactions displayed in the MDTB identified several subsets of defensive behaviors that may ultimately represent different emotional states.

Drug experiments demonstrated that anxiety-relieving compounds generally tend to decrease defensive behaviors. However, note that some responses are specifically or mainly affected by certain drug classes. Thus, BZPs decreased RA activities of mice chased by the rat and defensive threat and attack responses, whereas the serotonin agent gepirone mainly affected contextual defense and defensive threat and attack behaviors. In addition, SSRIs, MAO inhibitors, and CCK_B antagonists have a clearer impact on flight responses than on other defensive reactions. Together, these observations suggest that RA, flight, defensive threat–attack, and escape attempts probably reflect different aspects of anxiety-related reactions, thereby confirming the findings from the factor analysis.

Clinical Relevance of the Defensive Behaviors of the Mice

The factor analysis and the results from the drug experiments lead to the possibility of finding components of defense that are similar to human anxiety reactions.

Risk assessment. Previous reports have suggested that there may be an isomorphism between RA responses in rats and several behaviors often

described in GAD patients (D. C. Blanchard et al., 1991) such as apprehensive expectation and vigilance and scanning, involving hyperattentiveness (*Diagnostic and Statistical Manual of Mental Disorders* [*DSM–IV*]; American Psychiatric Association, 1994). With the exception of gepirone, drugs effective against GAD (i.e., BZPs) modulated this particular response. Importantly, anxiolytic drugs that affect RA generally decreased the response in situations where baseline scores were high (i.e., the chase test), whereas they increased RA when control activities were low (i.e., straight alley test). Together, these findings indicate that there is a rather good correspondence in terms of drug effects between the clinical outcome in GAD and the ability to modify RA responses in the MDTB. This strongly suggests that the latter behavior may be considered particularly relevant in modeling some aspects of GAD.

Flight. The observation that PD patients usually report an urgent desire to flee from where the attack is occurring (American Psychiatric Association, 1994) has led several authors to suggest that panic symptoms are due to pathological, spontaneous activation of neuronal mechanisms underlying flight reactions (Deakin & Graeff, 1991; Deakin, Guimaraes, Wang, Hellewell, & Hensman, 1991; Graeff, 1990). In accordance with this suggestion, data from the MDTB clearly demonstrated that panic-modulating agents specifically decrease animals' flight responses. Thus, the clinically effective antipanic agents reduced flight behaviors. Similarly, the putative antipanic compounds befloxatone, PD 135,158, and LY 288513 significantly decreased flight. Furthermore, the anti-GAD agents chlordiazepoxide, diazepam, and gepirone failed to affect this response in a selective manner (i.e., at nonsedative doses). Together, these findings suggest that flight reactions elicited by exposure to a natural predator may serve as an effective experimental model of panic.

Defensive threat and attack behaviors and contextual escape attempts. Although no isomorphism between these defense behaviors and a given symptom in anxiety-related disorders is indicated, the results indicate that these responses are particularly sensitive to modulation by drugs used in the treatment of GAD.

Conclusion

The MDTB studies suggest that this laboratory procedure provides a model capable of responding to and differentiating anxiety-relieving drugs of different classes through specific profiles of effect on different measures. This represents a significant improvement over other animal models for evaluating drugs active against emotional disorders and is consonant with the view that such disorders may represent dysfunction in particular defense systems.

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