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Differentiation of Anxiolytic and Panicolytic Drugs by Effects on Rat and Mouse Defense Test Batteries

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BLANCHARD, R. J., G. GRIEBEL, J. A. HENRIE AND D. C. BLANCHARD. *Differentiation of anxiolytic and panicolytic drugs by effects on rat and mouse defense test batteries*. NEUROSCI BIOBEHAV REV **21**(6) 783–789, 1997.—The use of ethoexperimental techniques to elicit and maximize the full range of defensive behaviors of rats and mice enables a very precise analysis of the effects of drugs on these behavior patterns. Two rat defense test batteries (the fear/defense test battery or F/DTB and the anxiety/defense test battery or A/DTB) have provided evidence that anxiolytic drugs, even from different classes, produce a common pattern of changes in specific behaviors. A recently developed mouse defense test battery (MDTB) has enabled description of mouse defensive behaviors to a predator, for comparison to those of rats, and a series of studies of drug effects on the behaviors measured in the MDTB provides evidence of cross-species generality of anxiolytic drug effects, or lack of effect, on specific defensive behaviors. In addition, tests with panicogenic and panicolytic drugs in the MDTB indicate that these enhance and reduce, respectively, flight reactions, which generally are not altered by anxiolytic compounds. Thus, results from the MDTB, taken in conjunction with those of the two rat test batteries and other defense analyses in rats and mice, provide evidence that many defensive behaviors are similar across rodent species, while the differences obtained provide a consistent pattern across situations. Moreover, the defense test batteries may be used to differentiate the effects of drugs effective against generalized anxiety as opposed to panic, through effects on specific defensive behaviors. © 1997 Elsevier Science Ltd.

Rat Mouse Defense test battery Anxiety Panic Benzodiazepine Serotonin Defensive behavior Flight Risk assessment

THE suggestion has been made many times that the defensive behaviors of lower mammals constitute a significant model for understanding human emotional disorders (5,6,21,24,39). Defensive behaviors tend to be quite similar across mammalian species in terms of their antecedents, i.e. threatening conspecifics or predators, or dangerous situations (28), their form or type (6) and their effect on the threat situation (1,2,21). If these commonalities extend across the spectrum of mammals, then the neurobehavioral systems controlling defensive behaviors of laboratory animals such as rats and mice may be, to a considerable degree, homologous to those of humans.

This view is supported by recent analyses of the neural systems involved in specific defensive behaviors, which suggest that these also are strikingly similar across mammalian species (4). Neural systems research also indicates that particular defensive behaviors (freezing, flight, defensive vocalization, defensive attack), can be differentiated anatomically (for reviews, see (1,4,25,37)), suggesting that they should be viewed as separate but related neurobehavioral systems.

If the target symptoms of human emotional disorders are related to particular defensive behaviors (e.g. (26,39)) then a specific strategy in analysis of the pharmacology of a given disorder is suggested: first, determination of profiles of change in the fullest possible spectrum of defensive behaviors, in response to compounds that appear to produce, or to alleviate, that disorder in humans. Second, if a relatively consistent profile of change can be established for drugs with common action against a particular clinical disorder (or in inducing its symptoms), this profile of effects on defense may be used to provide a much more specific animal model of the disorder. Such specific models should facilitate preclinical research on drug therapies and also provide the possibility of more sophisticated analyses of the relationships among emotion-linked disorders. Such profiles of drug effects can additionally be used as a component of further research efforts to establish functional relationships between drugs, including analyses of the role of individual receptor subtypes in the control of particular responses or profiles of response.

1. CHARACTERIZATION OF DEFENSIVE BEHAVIORS

Studies using a visible burrow system (VBS) affording both a burrow (tunnel/chamber) system and an open, or

'surface' area, have been used to characterize the overall pattern of defensive behaviors of rats and mice to a cat, over a 24-h period following cat exposure. In this situation, as in others (3), the behaviors of cat-exposed rats are systematically changed for 24 h or more (12). The initial defensive reaction is flight to the burrows, followed by freezing for 30 min or more, typically with ultrasonic vocalizations at about 22 kHz (13). Movement in the burrow system resumes over the next 4 h, and avoidance of the open area where the cat was encountered gives way to a pattern of risk assessment activities oriented toward this area. Risk assessment is defined in terms of orientation toward potential threat, often followed by specific approach responses, along with the assumption of a 'flat back' or stretched body orientation ('stretch attend') and approach toward the threat source ('stretch approach'). The more active risk assessment behaviors peak after freezing and avoidance of the open area have declined, typically some hours after cat presentation. Pinel *et al*. (43) demonstrated that these activities are associated with a gathering of information concerning potential threat sources. We regard risk assessment as a pivotal defensive behavior in both intense and mild threat situations, as it facilitates acquisition of information leading to intensified defensiveness and defensive behavior (if the threat stimulus is found) or to decreased defensiveness and defensive behavior (if the threat stimulus is consistently not found). Inhibition of non-defensive behavior, such as eating, drinking, and sexual and aggressive activity, is seen for up to 24 h following a single cat exposure. Less intense threat stimuli (e.g. novel object) elicit the same sequence, but the initial avoidance is short, and risk assessment and inhibition of non-defensive behaviors are the major defensive behaviors seen.

Following cat exposure in the VBS, mice show a pattern that is, in all but two respects, identical to that of rats (18). These differences are, first, that mice show neither sonic or ultrasonic cries in this situation. Second, each mouse, unlike a rat, needs to see the cat for itself: when the cat is presented, each mouse approaches the tunnel opening to scan the cat several times before retreating to the burrows and re-emerging only 20 h or so later. In contrast, rats, even those that have not seen the cat, will freeze in the burrows on cat presentation, a period in which high magnitude ultrasound production is heard. The hypothesis that this early risk assessment behavior by mice exposed to a cat reflects the lack of ultrasonic alarm cries in this species is supported by recent findings (unpublished results) indicating that, when mice are confined to the surface with the cat before being released to run into the burrows, such risk assessment does not occur. The released animal retreats directly to the burrows and freezes there. Our ongoing studies of mouse defensive behavior also suggest less suppression of non-defensive behaviors (aggression, eating, etc.) during predator exposure. This is consonant with the lack of initial suppression of risk assessment after cat exposure, and further simplifies the mouse pattern, compared to that of the rat.

These differences between laboratory rats and mice may be related to differential domestication of the two species. There are reasons to believe that the laboratory mouse generally has not been so severely selected on the basis of its defensive behaviors as has the rat. The smaller size of the mouse and its reduced potential to make serious wounds, plus the ease of handling mice with a tail pickup, enable greater human tolerance of defensive threat and attack behaviors in this species. Moreover, domesticated mice often do show biting behavior to human handling, consonant with a view that biting mice have not been systematically removed from the breeding pool. Thus, Swiss–Webster mice, confronted with an approaching threat stimulus (laboratory rat), show initial flight, followed by freezing and defensive vocalization and biting, the latter only when escape is blocked (17). These defense patterns closely resemble those of wild rats, and indicate that mice of this strain do not show the reductions in flight and defensive threat/attack that are typical of laboratory rats. Consonant with previous findings that 'emotional' behaviors differ substantially among mouse strains (e.g. (46)), in the same study (17), C57/BL6N Sin mice displayed a pattern of responses more similar to that of laboratory rats, suggesting that the Swiss-Webster mouse may be a more suitable subject than the C57/BL/6N Sin strain for studies concerned with defensive behaviors.

2. THE DEFENSE TEST BATTERIES

These analyses were followed by the creation of test batteries in which particular defensive behaviors can be individually elicited and their response to drugs determined. The fear/defense test battery (F/DTB) measures rat reactions (flight, freezing, defensive threat and defensive attack) to an approaching and contacting predator, whereas the anxiety/defense test battery (A/DTB) primarily measures risk assessment and inhibition of non-defensive behavior to potential threat. The labels for these test batteries (fear/ or anxiety/) reflect the traditional psychological view that fear is associated with the presence of actual danger, whereas anxiety involves the anticipation of an aversive event (29,30). However, the test batteries were devised simply to measure defensive behaviors to two different types of threat stimuli: either a present predator or situations and other stimuli associated with a predator. The focus of analysis in each situation was on specific behaviors, and not on some combined or overall measure taken to represent 'fear', 'anxiety' or any other theoretical construct.

The more recent mouse defense test battery (MDTB) combines many of the features of the F/DTB and the A/DTB into a single procedure, eliciting and measuring reactions to both present and anticipated threat. In a mouse-scaled oval runway, Swiss–Webster mice show an extremely precise delineation of defensive behaviors, including flight, avoidance, sonic vocalization and defensive threat/attack, with each behavior controlled by specifiable characteristics of the threat stimulus and situation, just as in rats. As in the VBS, the major mouse difference from rats is in risk assessment. During flight, mice stop periodically and look back at the approaching predator: also, mice trapped in the runway often show approach/withdrawal activities toward the predator. Such early (i.e. to the predator rather than after the predator has been removed) risk assessment activities are extremely infrequent in rat tests, which is consonant with the VBS findings that mice, but not rats, show risk assessment activities while the predator is actually present.

All three test batteries can demonstrate bidirectional change, a prerequisite for contemporary animal models of anxiety (23,38). As these tasks use a non-attacking predator

as the threat, analyses of drug effects are not contaminated by reactivity to shock or pain, while learning/memory effects are also minimized. Moreover, in both the F/DTB and the MDTB, sedative/myorelaxant as well as anxiolytic effects can be evaluated through analysis of various locomotor measures, permitting determination of levels at which either 'pure' anxiolytic effects, or sedative/myorelaxant effects (with or without anxiety reduction) occur. Such evaluation is also possible in the A/DTB, but the procedure involves comparison of changes in various behaviors, rather than the direct use of index measures.

3. DRUG EFFECTS ON THE THREE RODENT TEST BATTERIES

3.1. A/DTB and F/DTB

Blanchard *et al.* (21) summarized studies of drug effects in the A/DTB and the F/DTB. The only behaviors showing a relatively consistent response to anxiolytic drugs in the F/DTB were defensive threat/attack reactions, which declined after administration of clinically effective benzodiazepine (BZP) and serotonin receptor (5-HT_{1A}) ligands (9,10). However, these responses showed a bidirectional (increase at low doses, decrease at high doses) response to alcohol (14), such that, if alcohol is accepted as an anxiolytic, which is strongly indicated by other test results, reductions in defensive threat and attack cannot be regarded as unequivocal measures of anxiety reduction.

In contrast, in the A/DTB, four behavior changes were seen with anxiolytic drugs: reductions in proximic avoidance and behavioral inhibition; and increased risk assessment when this was measured in a freezing context in which risk assessment is normally suppressed, but reduced risk assessment in less threatening situations in which risk assessment is a component of baseline (control) behavior. These changes (three or more of the four) occurred in response to drugs effective against clinical anxiety (e.g. (7,19)) and also to alcohol (15,16). Two additional compounds that have not been tested in a clinical context, the 5-HT_{1A} receptor agonist 8-OH-DPAT (11) and the non-competitive NMDA antagonist MK-801 (8), also showed this profile of effects. A variety of drugs without any important anxiolytic effects (e.g. ritanserin, acute alprazolam, morphine) did not show such effects, and it is notable that the 5-HT_3 receptor antagonists ondansetron and MDL 72222 also failed to affect the elements of the 'anxiolytic profile' (all reviewed in (21)). A number of these effects (diazepam, chlordiazepoxide) and failures to find effects (ritanserin) have recently been replicated in a runway containing a shock prod and measuring 'stretched approach posture' and 'intention movements' (40). The same study obtained similar effects from additional drugs of particular classes (e.g. 5-HT_{1A} agonist; flesinoxan and ipsapirone) that showed effects on these measures in the A/DTB.

A major element of the 'anxiolytic profile', the bidirectional effect of anxiolytics on risk assessment as a function of baseline behavior, is consistent with the dynamics of the defense pattern and its diminution over time for rats in the VBS. In a high-threat context (i.e. soon after cat presentation), the predominant mode of response is freezing and avoidance: factors decreasing defensiveness (e.g. passage of time without further threat in the VBS or, administration of anxiolytic drugs in the A/DTB) act to increase risk assessment in such situations. However, in a low-threat situation (e.g. to cat odor alone, or hours after cat exposure in the VBS) in which risk assessment is expressed as the dominant defensive response, the same factors act to decrease risk assessment and return the subject to a 'normal' largely non-defensive behavioral mode.

3.2. MDTB

Findings from the A/DTB provided the basis for predicting that anxiolytic drugs would affect risk assessment behaviors in the MDTB. However, the mouse VBS finding of risk assessment to a present predator suggested that anxiolytic compounds would reduce risk assessment to present as well as potential threat, because, unlike rats, mice fail to show an initial period in which risk assessment is suppressed. In addition, the MDTB permits rapid determination of dose levels at which changes in defensive behaviors are, or are not, attributable to myorelaxant or sedative effects, thus indicating which levels produce specific defense effects. Thus, the following descriptions typically involve only dose levels at which specific effects were obtained (i.e. effects of motor-impairing doses are generally not described), and, unless otherwise noted, present only statistically significant ($p < 0.05$ in comparison to relevant controls) findings. Research using the MDTB has focused on three different classes of drugs: benzodiazepine receptor (BZPR) ligands, direct serotonergic (5-HT) ligands and 5-HT reuptake inhibitors (SRIs).

3.2.1. Benzodiazepine receptor (BZPR) ligands

The BZPR full agonist chlordiazepoxide (CDP), at non-myorelaxant/sedative doses (5 and 10 mg/kg) reduced only risk assessment measures (stopping, orientation to the predator, and reversals during flight from the chasing predator), and defensive bites. Notably, the highest CDP dose (25 mg/kg) altered many additional defense measures but also increased falls and decreased top running speed, thus showing agreement on two measures of myorelaxation (35). Both of the specific effects of CDP (i.e. those seen at non-myorelaxant doses) were consonant with previous rat results (21), suggesting considerable across-species generality for drug effects on particular defensive behaviors.

These data represented part of an initial attempt (32) to analyze the role of the benzodiazepine receptor (BZPR) in the modulation of MDTB behaviors. Other compounds used were Ro 19-8022, a non-BZP BZPR partial agonist (0.5–2.0 mg/kg), the BZPR antagonist, flumazenil (5.0–20.0 mg/kg) and the BZPR inverse agonist, Ro 19-4603 (0.025–0.01 mg/kg), as well as both single and repeated injections of the triazolobenzodiazepine alprazolam. A composite of risk assessment measures for these compounds (see Fig. 1) indicates that Ro 19-8022 also strongly reduced risk assessment behaviors, whereas the antagonist failed to affect, and the inverse agonist increased, these same behaviors. At non-sedative doses, acute alprazolam failed to alter risk assessment measures to the chasing predator, whereas chronic administration altered one of these measures.

Figure 2 presents defensive threat and attack for the same array of BZPR-active compounds. As would be predicted on the basis of rat data, Ro 19-8022 reduced these measures, whereas the inverse agonist potentiated them. The antagonist flumazenil had no effect on the defensive threat/attack

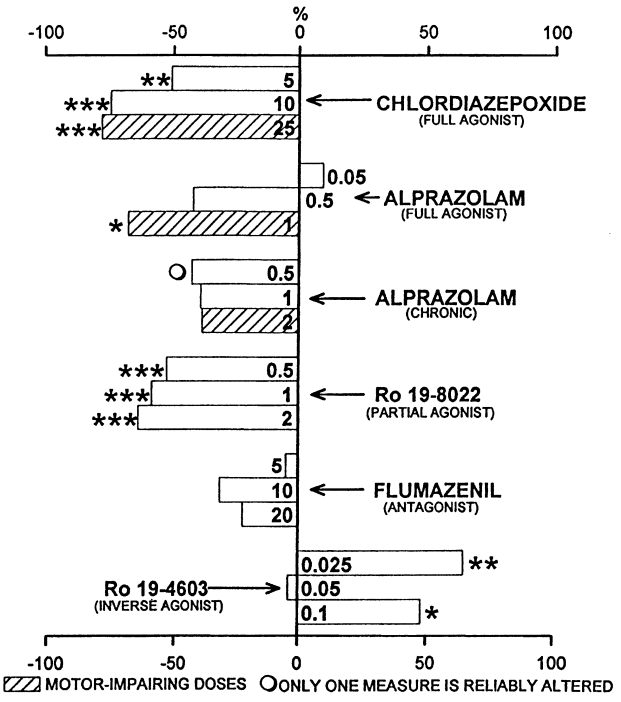

FIG. 1. MDTB: effects of BZP receptor ligands on composite risk assessment responses of mice chased by a natural predator.

composite, but did reduce one of the individual measures in the composite. Alprazolam also decreased the threat/attack composite following repeated, but not single, injection.

Thus, the effects of the various BZPR-active compounds on risk assessment and defensive threat/attack behaviors were quite similar: compounds that increased either of these also increased the other. The defensive threat/attack effects replicate F/DTB results for CDP and are consonant with other BZPR agonist (diazepam; midazolam) effects in that task (10), and the risk assessment-reduction effects are similar to those of diazepam in the cat odor component of the A/DTB, a test in which controls showed moderate levels of risk assessment (16). It should be emphasized again that the risk assessment effects of the BZPR agonist diazepam, in A/DTB tests in which risk assessment was minimal (i.e. in which actual cat exposure elicited freezing and proximic avoidance as predominant defensive behaviors), were to increase risk assessment, presumably by a release of the response-suppressive effects of these predominant defenses (7). This risk assessment reduction is directly opposite to the risk assessment-enhancement obtained in rats in situations in which low-level threat stimuli elicit risk assessment as a major defense. As mice do not show such early suppression of risk assessment to a predator, it is the latter effect, of reduced risk assessment, that was predicted for the MDTB.

This pattern of findings—with the effects of CDP and the partial agonist Ro 19-8022 reliable and similar, the effects of the inverse agonist reliable and in the opposite direction and the antagonist having no effect on one composite of measures and a relatively minor effect on the other—suggest that BZPR may be involved in both risk assessment and defensive threat/attack behaviors.

For both sets of behaviors, single injections of alprazolam had no effect, but repeated injections produced an agreement with the agonist pattern of decreased defensive threat/attack and (for one measure) risk assessment. However, the overall effect of alprozolam on anxiety-related measures was somewhat weaker than that of CDP.

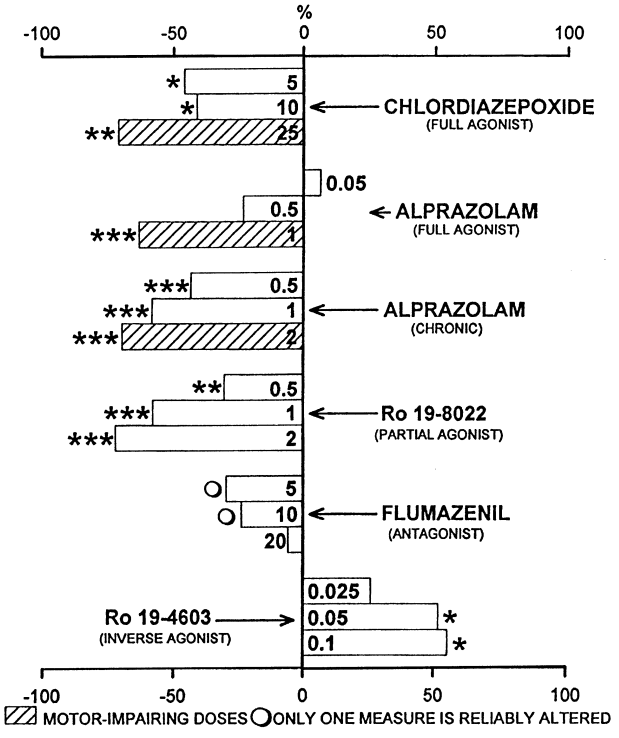

FIG. 2. MDTB: effects of BZP receptor ligands on composite defensive threat and attack responses of mice chased by a natural predator.

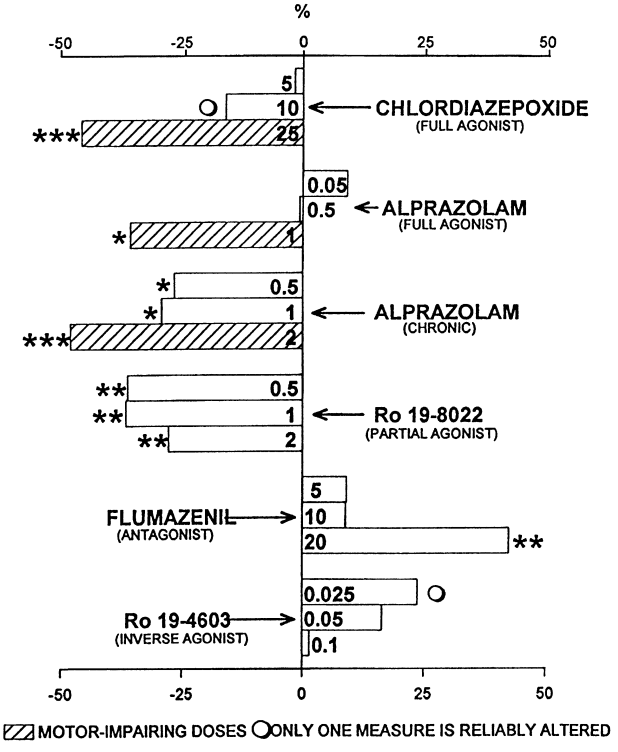

FIG. 3. MDTB: effects of BZP receptor ligands on composite flight responses of mice chased by a natural predator.

Because the rat results suggested that the classic BZPs do not alter flight behaviors, a flight composite was examined for the same array of compounds (Fig. 3). CDP and the single dose of alprazolam failed to alter the flight composite at non-myorelaxant levels, while the inverse agonist Ro 19-4603 also failed to alter the flight composite, although at the lowest dose, it did reliably alter one of the component measures. The antagonist, flumazenil, increased flight, an intriguing finding in light of reports (42) of the elicitation by flumazenil of panic attacks in eight of ten panic disorder patients. These results provide a very different profile from that predicted by specific action at the BZPR. However, the non-BZP BZPR partial agonist Ro 19-8022 reliably reduced flight at all doses, suggesting a somewhat wider spectrum of effects on defense for this non-BZP BZPR partial agonist than was obtained for full agonists given as single doses. Repeated injection of alprazolam strikingly reduced flight measures.

Thus, for CDP, the (negative) results for flight as well as the (positive) risk assessment and defensive threat/attack effects obtained in the MDTB were completely in agreement with findings from the rat test batteries, and with other tests involving similar risk assessment measures (40). Moreover, the MDTB single-injection alprazolam results were in agreement with the failure to find effects of (single) alprazolam injections in rat tests (21).

3.2.2. Panicogenic and panicolytic drugs

The MDTB also may provide a profile of effects that respond selectively to panicolytic or panicogenic drugs. Our first MDTB study (20), using an early and somewhat different version of the test, involved the panicogenic agent yohimbine (0.5, 1.0 and 2.0 mg/kg). This compound potentiated avoidance, reactivity to dorsal contact, and contextual defense (escape), but reduced freezing, suggesting that panic may involve a different set of defensive behaviors (primarily flight/avoidance) than does anxiety. This prediction was tested with the later (and current) version of the MDTB, using single and repeated injections of alprazolam (34), and of the antipanic (41,45) agents, imipramine and fluoxetine (31). Figure 4 provides flight results for the latter two compounds: effects of single and repeated injections of alprazolam on flight were presented in Fig. 3.

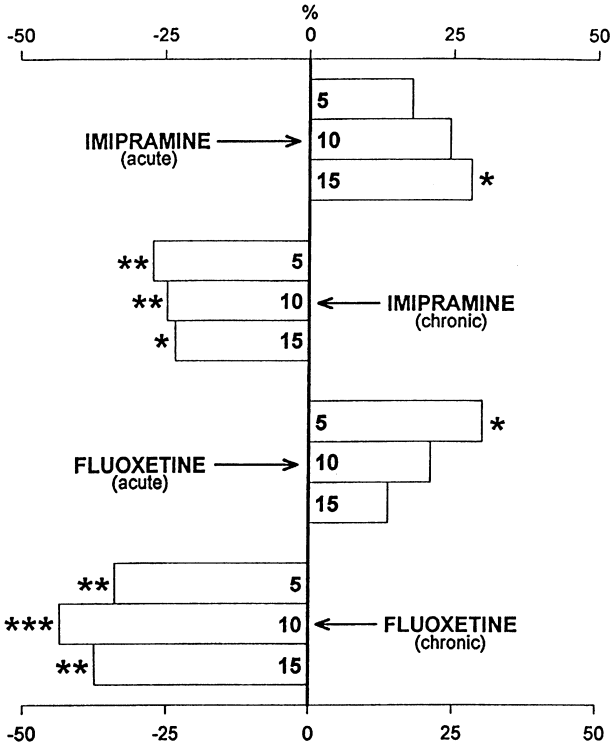

FIG. 4. MDTB: effects of acute or chronic administration of 5-HT reuptake inhibitors on flight responses of mice to a natural predator.

As with alprazolam, repeated but not single administration of imipramine and fluoxetine reliably reduced flight responses. Whereas the single injection of alprazolam had no effect, single injections of imipramine or fluoxetine reliably increased flight (as well as defensive threat/attack, not shown). It is notable that all three compounds, given on a repeated basis, are effective against panic (22,27,41, 44,45,47). These data are also consonant with the transient increase in anxiety often reported at the beginning of treatment with serotonin reuptake inhibitors in panic disorder patients (e.g. (48)). In addition, a specific connection between panic and flight is supported by the finding, noted earlier, of increased flight following flumazenil, a substance that may induce panic attacks in panic disorder patients (42).

Administered on a repeated basis, both imipramine and fluoxetine also changed several other defensive behaviors, with a pattern considerably similar to that of the BZPR agonists: decreased defensive attack, and reduced risk assessment during flight from the oncoming predator, but no change in risk assessment measures to the approaching predator. Although fluoxetine has not been tested in the cat odor test of the A/DTB, another SRI, fluvoxamine, as well as imipramine, produced decrements in similar ('stretch attend' or 'intention movement') measures in a straight alley situation utilizing a discrete shock stimulus rather than the cat odor (40).

3.2.3. 5-HT receptor ligands

Because the 5-HT_{1A} receptor agonists, 8-OH-DPAT and gepirone provided anxiolytic profiles in the rat A/DTB, they were also evaluated in the MDTB (33). The highest dose level of 8-OH-DPAT (10 mg/kg) had motoric effects. However, at levels that did not impact motor function (8-OH-DPAT at 0.05, 0.5, and 1.0 mg/kg; gepirone at 2.5, 5.0 and 10.0 mg/kg), both drugs reliably reduced the frequency of approaches to and withdrawals from the oncoming predator, a group of risk assessment measures different from those impacted by the BZPs. Both compounds reduced defensive bites in the MDTB, a finding consonant with that of gepirone in the F/DTB (8-OH-DPAT was not tested in the F/DTB). Thus, like CDP, the 5-HT_{1A} receptor agonists produced effects in the MDTB that were highly similar to their effects in the F/DTB (reduced bites) and the A/DTB (altered risk assessment).

The administration of pirenperone (0.5–2 mg/kg), a preferential antagonist at the 5-HT_{2A} receptor, reduced all flight parameters, including number of avoidances, avoidance distance and flight speed even at the lowest, and only, dose without motoric effects (33). In sharp contrast, the drug had no reliable effect on any risk assessment measures or on defensive threat and attack behaviors.

Some additional 5-HT receptor ligands, such as S 21357, a mixed 5-$HT_{1A,2A}$ receptor antagonist (0.12, 0.5, and 2 mg/kg) have now been used in the MDTB (36). This compound also reduced risk assessment and defensive attack behavior, consistent with the behavioral changes seen to 5-HT_{1A} receptor agonists. However, S 21357 also strongly reduced flight reactions, suggesting, as do the pirenperone (33) flight findings, a relationship between antagonism of the 5-HT_{2A} receptor and reduction of flight. Whereas the flight/avoidance effects of S 21357 in the MDTB were very similar to those of pirenperone, it is notable that all compounds with important effects at the 5-HT_{1A} receptor that we have tested affected risk assessment, whereas pirenperone did not.

4. DISCUSSION

These studies extend the rat analysis to another mammalian species, indicating, first, that with the exception of ultrasonic vocalizations to threat, absent in the mouse, the defensive behaviors of rats and mice are very similar. However, as with wild-laboratory rat comparisons, mice and rats do differ in terms of the prevalence or potency of specific defensive behaviors, with mice of the Swiss–Webster strain (and likely some other laboratory mouse strains) less 'domesticated' than are laboratory rats. Another quantitative difference, again possibly related to the stronger suppression of behavior shown by laboratory rats in threatening situations, is that mice, but not rats, show a strong initial risk assessment tendency early in their confrontations with a predator.

Of these three defense differences of rats and mice, the last is most important in terms of analysis of behavior in the MDTB. The active risk assessment (orientation and approach) of mice to a present predator precludes the specific component of the rat 'anxiolytic profile' that involves increased risk assessment in highly threatening situations in which risk assessment does not normally occur, leaving an unequivocal prediction that anxiolytic drugs should reduce risk assessment behaviors in mice, even during confrontation with a predator. The MDTB study results were fully consonant with this prediction, with each anxiolytic drug used in the MDTB producing a reduction in some aspect of risk assessment. It is intriguing and puzzling, however, that the BZP-active anxiolytics and the 5-HT_{1A} anxiolytics showed a considerable separation of which risk assessment behaviors were affected. Although the BZPR agonists did show some tendency toward reduction in the straight alley risk assessment measures, this was not significant, and these compounds significantly reduced risk assessment only to an approaching rat in the oval runway. In contrast, the 5-HT_{1A} anxiolytics reduced risk assessment behaviors to the rat only when the subject was trapped in the straight alley. Whereas these findings serve to confirm and emphasize a central role for risk assessment in anxiety, they also suggest the possibility of important differences between anxiety that is responsive to BZPR agonists as opposed to anxiety responsive to 5-HT_{1A}-active drugs, a possibility that has been relatively little investigated on the human level. In this context, it is also intriguing that the risk assessment behaviors changed by repeated administration of the SRIs imipramine and fluoxetine were more similar to those altered by BZPR agonists than to those responding to 5-HT_{1A} agonists.

The series using BZPR full, partial and inverse agonists, plus a BZPR antagonist, provided an initial assessment of the ability of the MDTB and its measures to indicate whether action at a particular receptor may be particularly involved in individual defensive behaviors. It is notable that risk assessment and defensive threat/attack behaviors, the two sets of behaviors most clearly responding to BZPR full agonists, such as CDP in both rat and mouse tests, both showed an appropriate response to drugs with agonist, antagonist or inverse agonist action. Repeated administration of alprazolam produced a weaker effect, but one that was consistent with the changes on these same measures with CDP. The view that the BZPR may be involved in these particular behaviors clearly needs to be further evaluated by determination of the effects of BZPR antagonists on these agonist and inverse agonist effects.

MDTB findings also indicate that compounds known to be effective in eliciting/exacerbating (yohimbine) or alleviating (chronic alprazolam, imipramine and fluoxetine) panic may enhance or reduce, respectively, flight behaviors, which are the same behaviors independently hypothesized to be involved in panic (26). Thus, MDTB results for both anxiolytic and panicolytic drugs showed an excellent agreement with predictions made on the basis of rat results (for anxiolytic drugs), or, on previous mouse studies with a panicogenic drug, yohimbine, for the panicolytic agents. These results indicate that specific effects on defensive behaviors can differentiate drugs that are active against panic as opposed to generalized anxiety disorder, providing general confirmation of a major premise of the view that defensive behaviors represent a significant, and possibly homologous, model for understanding emotional disorders.

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