ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 54, No. 1, pp. 13-20, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02176-0

Exploration and Predation Models of Anxiety: Evidence From Laboratory and Wild Species

C. A. HENDRIE,*[1] S. M. WEISS* AND D. EILAM†

*Department of Psychology, University of Leeds, Leeds LS2 9JT, West Yorkshire, UK
†Department of Zoology, University of Tel-Aviv, Ramat-Aviv, 69 978, Israel

HENDRIE, C. A., S. M. WEISS AND D. ELIAM. *Exploration and predation models of anxiety: Evidence from laboratory and wild species.* PHARMACOL BIOCHEM BEHAV **54**(1) 13-20, 1996.—The current article addresses several issues within the context of modeling human anxiety disorders in the laboratory. First, evidence is presented to support the suggestion that behavior in exploration models of anxiety may be motivated by apprehension relating to intraspecific encounters rather than interspecific, predator/prey interactions, which has consequences for the interpretation of findings generated using these tests. Second, data are reviewed concerning the use of stimuli indicating the presence of a predator in the context of anxiety modeling, and it is suggested that tests involving the reactions of animals following exposure to such stimuli may be more closely related to pathologic anxiety mechanisms than tests employing observations during contact with these stimuli. Third, comparative studies, using wild-caught rodents, are outlined that show that, although there are similarities in the defensive strategies adopted by these animals in response to the call of an owl, there are also important differences. Finally, the suggestion is made that the distance-dependent-defense-hierarchy may be of important heuristic value in the interpretation of these data and that, perhaps more significantly, it may also provide a mechanism that allows animal defensive strategies and human anxiety disorders to be placed within the same conceptual framework.

Predation Owl calls Anxiety Plus-maze Black/white exploration model
Distance-dependent-defense-hierarchy Wild animals Rats Mice

ANXIETY in human populations may be seen as both a normal and pathologic condition with both types potentially leading to medical or professional help being sought. In the normal situation, anxiety appears to be related to a fairly specific event, life crisis or threat, while its pathologic form is characterized by unrealistic or excessive apprehensive expectation concerning events that may occur (33). Similarly, in animals, anxiety may be seen as either a normal or a pathologic state. In captive predator species, for example, stereotyped pacing within the confines of a cage is often observed and engenders empathic sympathy in human observers. However, in a different situation, the permanent states of anxiety aroused in these predators' prey in the wild is not only regarded as normal but as a necessary process within the evolution of strategies designed to ensure survival (12).

Human anxiety disorders are clearly a major world health problem, as, at any one time, 2-4% of the population may be diagnosed as having one or another aspect of this disorder. Further, 40% of world sales of psychoactive drugs are anxiolytics, which accounts for an annual turnover in excess of 2.5 billion pounds Sterling (39). Therefore, there are clear therapeutic and economic pressures to develop adequate models adapted for the discovery and prediction of novel agents for the treatment of anxiety in the clinic and to develop a greater understanding of the mechanisms involved.

ANIMAL MODELS OF ANXIETY

To date, the assumption underlying most animal models of anxiety is that anxiety/defense mechanisms are essential for survival, and are, hence, a feature of, at the very least, mammals. Animal and human anxiety states are, therefore, viewed as being on a continuum and mediated by similar mechanisms. As such, it is appropriate to examine the effects of drugs on the anxious behaviors of animals to predict the potential utility of these drugs in the treatment of human disorders. In this context a number of animal models have been developed, which may generally be divided into three distinct categories: a) those that involve unconditioned responses such as the hole-board test (13), light/dark exploration model (9), and elevated plus-maze (34); b) conditioned avoidance responses, such as the four-plate test (6), conditioned suppression [see (16) for review], and the Geller-Seifter conflict test (15); and c) other

[1] To whom requests for reprints should be addressed.
Article published without the benefit of author corrections.

conditioning models, such as potentiated startle (10) and conditioned defensive burying (40). The purpose of each of these models is to attempt to activate endogenous anxiogenic mechanisms and to examine these under drug and drug-free conditions to uncover their mediation. Hence, drugs are developed on the basis of their ability to attenuate expressed anxiety under controlled conditions in various test procedures that are viewed as having some relationship to anxiety states in humans.

CONDITIONING MODELS

Conditioning models involve the pairing of an unconditioned response with (usually) an aversive stimulus and, therefore, may model reactions to specific aversive events (or a stimuli paired with these). As such, the etiology of anxiety under these conditions may be comparable to normal anxiety in humans as pathologic anxiety states are characterized by the overreaction to events that do not normally constitute a threat (33). These procedures may also be viewed as modeling human anxiety disorders if it is accepted that the acquisition of pathologic anxiety states involves conditioning. However, by definition anxiety states involve the possibility of an aversive event occurring (DSM-IV, APA, 1994) rather than an actual event. Therefore, as operant procedures rely on the pairing of an expressed behavior with an external event, it is difficult to see how this process may be usefully applied to mental events that are strictly internal. Nonetheless, such models are widely used and appear to have good predictive validity for the identification of known and novel antianxiety agents (17).

MOTIVATION IN EXPLORATION MODELS

In this context, exploration models, tests that rely on nothing more than the topology of the apparatus, may have direct parallels with human anxiety disorders. Of the numerous examples of these models, the elevated plus-maze and the black/white exploration test are among the most popular, with in the order of 100 articles being published in each of the 5 years of this decade so far. In these models, test animals show differential levels of activity in each of two areas that may be considered protected and unprotected. In the elevated plus-maze the former is represented as a closed arm, while in the black/white exploration model this is a dark area. Animals show a preference for protected areas under control conditions, and drugs that block this effect are indicated as anxiolytics. It is held that these alterations in locomotor patterning may be due to changes in the animal's cognitive appraisal or risk assessment (38) of the likelihood of potential predatory attack (11). These models also show good predictive validity for anxiolytics (17). However, in spite of the above assertion, the proposed spontaneous fear that proportedly motivates behavior in these models remains unidentified [e.g., (41)].

To propose that anxious behavior observed in laboratory animals is due to their assessment of the possibility of predatory attack requires the assumption that these behaviors are a consequence of selection pressures exerted on the ancestral wild stock.

Unfortunately for this interpretation, there is no evidence to suggest that the behaviors seen in tests such as the black/white exploration model and elevated plus-maze relate, in any way, to potential predation. It has been shown by several groups that laboratory animals will react to stimuli indicating the presence of a predator [(3,18,21,27,28); see below]; however, these findings bear no relation to studies where such stimuli have never been presented. Therefore, it may equally be suggested that the activation of endogenous anxiogenic mechanisms in animal models may be due to fear of intraspecific, rather than interspecific interaction.

Laboratory animals given the opportunity to express their natural social organization rapidly differentiate into various identifiable groupings. Depending on the species, these are dominant, subdominant, and subordinate (e.g., rats) or territory-holding dominants and nonterritory-holding subordinates (e.g., mice). Subordinate animals may be easily identified as, in consequence of the permanent stress they are placed under, they appear bedraggled (2) and also develop an atrophy of the adrenopituitary and immune systems, which leads to an early demise (8). As such, when laboratory species are introduced to situations where they must compete for access to females and other resources, a large proportion of them show behavioral and physiological characteristics that may be viewed as being pathological. Figure 1 shows the cumulative bites received in a cage of mice left undisturbed for a period of 9 months. As can be seen, fighting is extensive, and, as within each cage there is one animal that is virtually un-

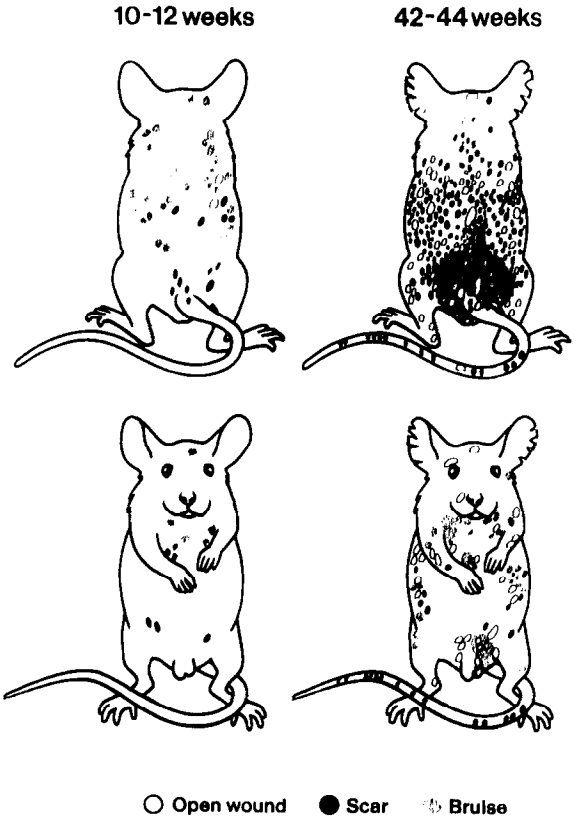

FIG. 1. Bite target analysis of young (10–12 weeks) and old (42–44 weeks) male DBA/2 mice. Cumulative bite target analysis of groups of 10 mice revealed that by the time animals had reached 42–44 weeks there was intense fighting within standard laboratory cages, as indicated by the number of open wounds, bruises from bites, and scars observed. As there was always one animal within each cage that was not significantly marked, it may be concluded that the levels of fighting seen may relate to attempts at territory formation under these conditions, indicating that laboratory mice retain characteristics that would increase reproductive fitness in the wild.

touched, it may be assumed that this individual is responsible for the damage in the others. In mice, territory holding is, under certain circumstances, a biological imperative and even in the restricted conditions of a laboratory cage they exhibit behaviors necessary to establish and retain such a reproductive advantage (19). Therefore, the possibility exists that in exploration models, animals show avoidance of certain areas as this increases the probability of agonistic contact with a territory-holding dominant. Anxiety may be a consequence of this and can be simply expressed as "this is not my territory, so it must be someone else's." Such an interpretation has intuitive appeal and enables a direct connection to be made between an animal's behavior and its recent social history. As such, the previous reliance on the proposed characteristics of an ancestral wild stock is rendered unnecessary.

In a study designed to test the above suggestion, that animals with experience of agonistic encounters would show more anxious-like behavior, DBA/2 mice were exposed to intraspecific encounters with either aggressive or nonaggressive territory holding males on six occasions. On the seventh occasion all animals were exposed to an aggressive resident in an open-topped cage and their behavior recorded over a 4-min period or until they had escaped from the cage. Data are summarized in Fig. 2 and show that latencies to escape from the open-topped cage are markedly reduced in animals previously exposed to agonistic encounter. These animals also received fewer bites. Behavioral analyses of animals, tested individually in an open field, revealed no differences in exploratory behavior of mice exposed to aggressive or nonaggressive residents. However there were marked increases in stretched attend postures, grooming, darting (from point A to point B), and body shaking in those previously exposed to aggressive residents. These data demonstrate that a history of social conflict reduces the latency to escape from another animal's territory and that a behavioral cluster indicative of increased anxiety is observed. Importantly, such agonistic encounters have also been shown to induced anxiogenic-like behavior in rats (20) and mice (37). In this latter study, it is particularly noteworthy that the scent of an aggressive resident alone produced significant effects, indicating that even in the absence of formal exposure to agonistic encounters, odors indicating the presence of a territorial male are an important signal for these animals. As such, these data together are consistent with the proposal that anxious-like behavior seen on exploratory models of anxiety may be a function of anticipation of intraspecific rather than interspecific encounters, which has consequences for the interpretation of results generated using these tests.

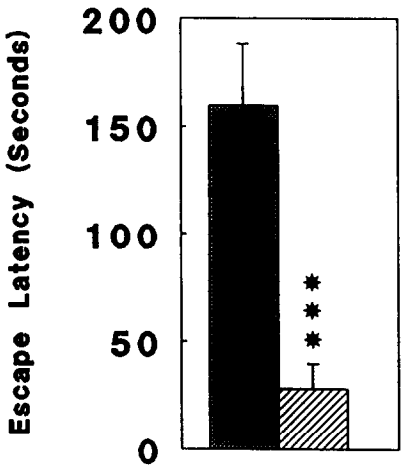

FIG. 2. Escape latencies from an open-topped cage following repeated exposure to social conflict. Data are presented as means (±SEM) of time taken to escape from a resident's home cage. DBA/2 mice were exposed to social interaction, by being paired with a nonaggressive individually housed conspecific or social conflict (paired with an aggressive resident) on six occasions. On the seventh exposure they were introduced into the open-topped home cage of an aggressive individually housed animal. Latencies to escape from this situation were then measured. Animals that had only been exposed to social interaction (dark bars) took significantly longer to escape as compared to animals that had previously been exposed to social conflict (light bars). These data, together with findings indicating that these animals also show an increase in stretched attend postures, grooming, and darting when paired with a nonaggressive individual on the seventh exposure, strongly suggest that there is an increased fear of intraspecific interaction in these animals. ***$p < 0.0001$.

PREDATOR MODELS

The utility of anxiety mechanisms in wild species may be clearly demonstrated. That is, that without adequate vigilance and antipredator defense mechanisms wild rats, and particularly mice, would rapidly become extinct as they are heavily predated upon. For example, Tawny owls (*Strix aluco*) have been shown to crop greater than 30% of a given woodland mouse population in a 2-month period, taking up to 8–10 per night (30). There are now many examples of predator models that include exposing test animals to a human (3), a cat or cat odors (4,27,28,31,42,43,44), and owl calls (21,24,25,26). Such models are similar in many aspects to conditioning models in that where animal behavior is assessed during exposure to a predator, this appears to relate to normal anxiety mechanisms, using an albeit more naturalistic stimuli. Further, the introduction of a predator species is often considered prima facea evidence to conclude that the reactions seen are related to predator defense. This assumption should only be accepted with caution in view of evidence that mice, for example, react not only to cat odor, but to almost every other novel odor they are exposed to (29).

However, some tests examine the behavioral consequences of having been exposed to a predator (4,5,25,26,44). This apparently subtle difference is of prime importance, as a direct relationship between stimulus and behavior is no longer being studied. Instead, under such circumstances, one is examining the cognitive consequences of having been exposed to stimuli indicating the presence of a predator. That is, in this test situation, animals are, in accordance with the DSM-IV definition of anxiety disorders, reacting to the possibility of an aversive event occurring in the absence of external cues indicating that this is likely. Further, the involvement of operant conditioning mechanisms may be excluded, as the presence of a predator (or stimuli indicating the presence of a predator) under laboratory conditions is always without behavioral consequence.

Extensive studies in this laboratory have examined the behavioral consequences of having been exposed to the call of a Tawny owl (21,24,25) and have shown that (a) owl calls, of a range of calls examined, specifically induce defensive reactions; (b) consummatory behaviors are suppressed by owl calls and endogenous analgesia mechanisms are activated by these;

and (c) the only drugs that have, thus far, been found to attenuate owl-call-induced defensive behavior are those that are also clinically prescribed antipanic agents (imipramine, alprazolam, and fluoxetine). These findings strongly suggest that exposure to owl calls induces behavioral reactions similar to panic in humans, as they are sensitive to the same variety of compounds. Further, cholecystokinin $(CCK)_4$, which has been shown to induce panic in humans (7), enhances panic-like behavior in animals exposed to owl calls, while CCK_B antagonists produce the opposite effect (22). The test procedure used to examine these effects involves exposing animals to 3 min of human voice, 2 min of owl call, then 5 min of silence. Animals are also given access to a small burrow, which serves as a strategically defensible location. These parameters were chosen to provide a period prior to exposure to an owl call in which the test animals may have the opportunity to habituate to the novelty of the situation. It is noteworthy that pilot studies have revealed that this period seems to be essential if experimental effects are to be observed. Without the 3-min precall period otherwise robust experimental effects are masked by what may be described as the exploratory imperitive displayed by these animals in the early stages of introduction to this and most other novel arenas. The 5-min silent period after exposure to the owl call mimics the hunting pattern of the owl, which, having made its territorial call flies to a hunting perch where it waits, in complete silence, to pounce or swoop on its prey. As such, test animals are provided with as much information indicating the presence of an owl as would be available to them in the wild.

Results of a meta-analysis from over 100 animals used as positive controls in studies to examine the effects of compounds with unknown effects are presented in Fig. 3. These data show a typical active-compound profile, where time spent in the strategically defensible burrow is largely unaffected by drug treatment during the voice and owl call periods, yet is markedly increased during the period of silence. Therefore, the interaction between drug action and having been exposed to an owl call may be clearly seen. Further studies have demonstrated that this effect is specific to owl calls and not merely an artefact of novelty. These data are presented in Fig. 4.

That animals do not, under drug-free conditions, spend increased time in the burrow upon hearing the owl call is in itself an interesting experimental finding. The explanation for this may relate to the patterning of defensive behavior along the distance-dependent-defense-hierarchy [D^3H] (14,36). Briefly, prey species are constantly vigilant to detect the presence of predators as early as possible. When a predator is detected, a prey animal takes immediate action to maximize the distance between it and the predator or to remove itself from visual contact. When the predator approaches rapidly, the prey species demonstrate various escape strategies, which may include freezing or running in a seemingly uncoordinated manner (protean behavior) (12). Finally, if the predator is at very close proximal distance, the potential prey may engage in defensive aggression, where it will attack using whatever natural weapons it possess. The behaviors seen at each stage are clearly discernable, and it has been postulated that the various phases of the [D^3H] may be mediated by mechanisms homologous to those underlying the heterogeneous class of disorders referred to as anxiety (25). Therefore, within this context, undrugged animals, once having heard the Tawny owl call, show high levels of defensive, escape-orientated, protean behavior (24). Animals treated with certain compounds show reduced levels of this behavior and, instead, show increased time spent in the strategically defensible burrow location. This effect clearly

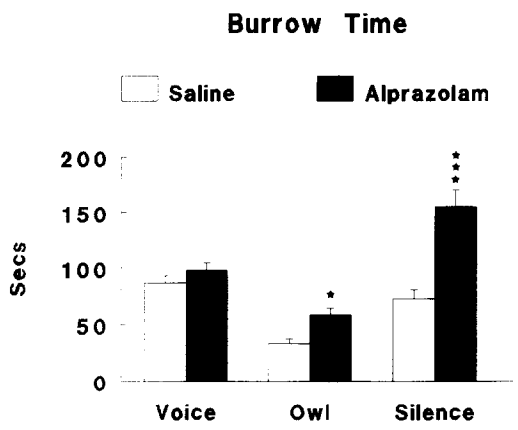

FIG. 3. Meta-analysis of the effects of 0.5 mg/kg alprazolam on burrow time in DBA/2 mice. Data are presented as means (±SEM) of time spent in a strategically defensible burrow location. Tests sessions were 3 min exposure to human voice, 2 min exposure to Tawny owl calls, followed by 5 min of complete silence. Alprazolam (Sigma, UK) was adminstered intrapertineally 30 min prior to testing. As can be seen, saline- and alprazolam-treated animals do not differ in the time they spend in the burrow during the human voice period. By contrast, animals treated with alprazolam, but not saline, show a modest increase in burrow time while the call is being played and a pronounced increase in burrow time during the period of silence, which represents the period of greatest danger, once having heard an owl call. These data are consistent with the proposal that protean escape behaviors seen in control animals in response to an owl call are replaced by a more organized defensive response, that is, hiding in the burrow. This response may be indicative of an antipanic action of alprazolam. $*p < 0.05$ $***p < 0.0005$ from control.

relates to the [D^3H] and demonstrates a lowering in intensity of the defensive reaction whereby protean behavior is replaced by more organized vigilance behaviors. As previously stated, of the compounds thus far examined, only clinically prescribed antipanic agents produce this effect. Therefore, this may reflect a parallel between protean behavior and human panic disorder.

Additionally, the above-outlined data provide strong evidence that behavioral reactions seen under these circumstances must involve an animal's interpretation of the probability of predatory attack. However, as laboratory animals have never been exposed to predatory attack, this appraisal is independent of its own direct experience and consequently, it is necessary to conclude that such reactions are innate. Therefore, a similar problem to that seen when considering results from exploration models arises. That is, it is necessary to invoke unsupported conceptualisations concerning the behavior of wild animals to interpret the behavior of laboratory species. To address this problem a series of studies were undertaken to examine the behavior of a number of wild-trapped species.

WILD ANIMAL STUDIES

There are a number of problems when examining the behavior of small rodents in the wild. First, it is almost impossible to observe their behavior directly, as they are often widely dispersed and almost always nocturnal. Second, extraneous factors, such as moonlight, have significant effects on the behavior of these animals, as the efficiency of their predators is increased (35). This factor also influences foraging patterns,

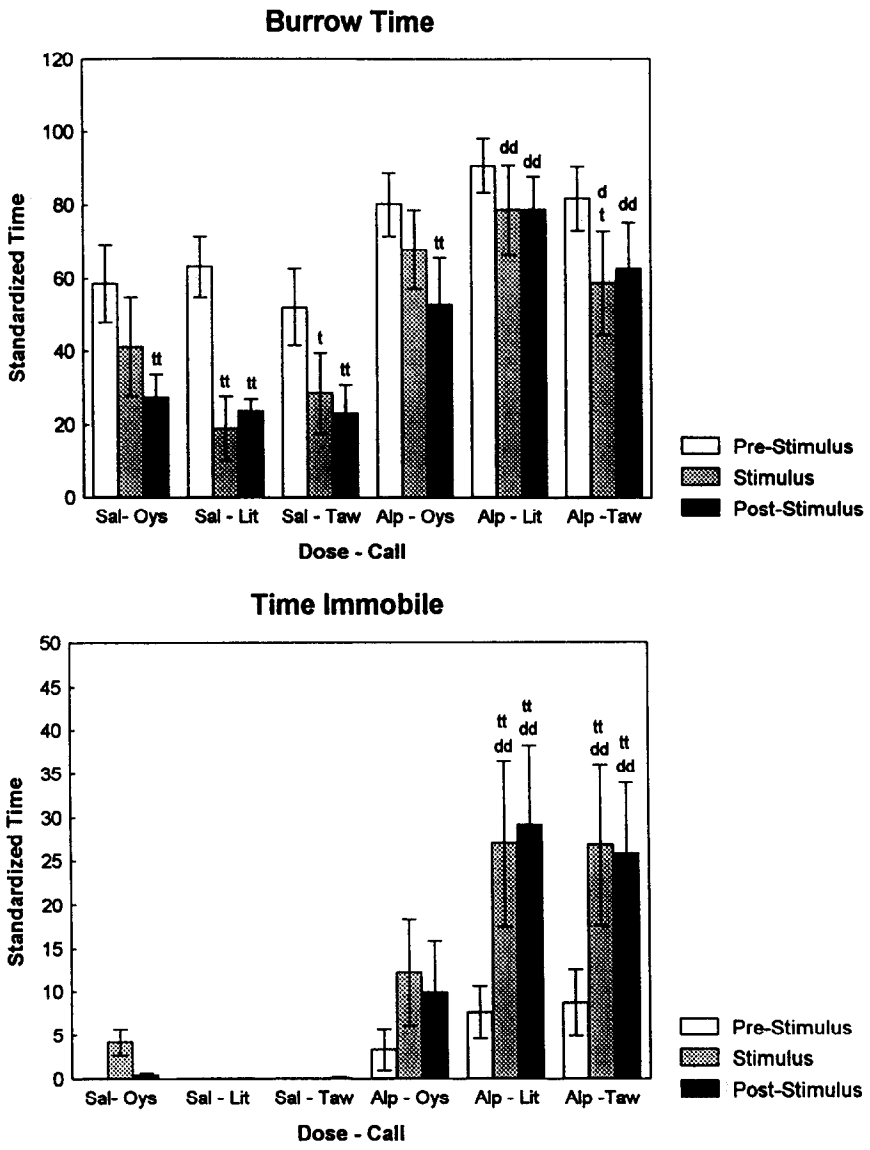

FIG. 4. Specificity of alprazolam/owl call interactions. Data are presented as means (±SEM) of time spent in the burrow (upper panel) or time spent immobile (lower panel) and are standardized as rates per minute to allow for the different time periods within the test session, which included a 3-min exposure to human voice (prestimulus), 2 min to test stimuli (stimulus), and 5 min of silence (poststimulus). DBA/2 mice were either exposed to the call of an oystercatcher (Oys) (nonmouse predator), Little owl (Lit), or Tawny (Taw) owl (predators) and treated with either saline (Sal) or 0.5 mg/kg alprazolam (Alp). All injections were given IP in a volume of 10 ml/kg 30 min prior to testing. Data reveal that when treated with saline all animals show a steady reduction in burrow time across the test session. This pattern is also seen in animals exposed to the oystercatcher call and treated with alprazolam. However, animals treated with alprazolam and exposed to the owl calls fail to show this pattern. The consequence of this is that during the period of silence, which represents the time of greatest danger once having heard an owl call, these animals spend a greater proportion of their time in the strategically defensible burrow location than oystercatcher controls. With regard to time immobile, the specificity of the alprazolam/owl call interaction becomes even clearer, as animals given saline show virtually no time immobile. Animals exposed to the oystercatcher call and given alprazolam show a similar response, but as can be clearly seen, animals exposed to owl calls and given alprazolam show marked increases in this measure. Together, these data indicate that the effects of alprazolam on replacing the expression of protean behavior with the more organized response of hiding in the burrow or remaining motionless are only seen following exposure to owl calls. $t = p < 0.05$ from prestimulus period. $d = p < 0.05$ from saline controls. Double letters indicate $p < 0.01$.

rendering observation yet more difficult. Third, the probability of an event of interest, such as an owl being present during observation periods, is low. As such, ecologists have developed ingenious approaches to resolve these difficulties. For example, owls and rodents of interest may be retained in large aviaries (in the order of 20 × 20 m) to overcome the problems of low density and chances of observing predator–prey interactions (32). Also, and perhaps more ingeniously, one group using hectare-sized enclosures has trained an owl to fly over the experimental plot from one experimenter to another. The problems of direct observation are solved by examining the distribution of footprints left by the rodent species of interest (1). Under such circumstances, desert rodent species have been found to markedly reduce their foraging ranges such that they are shifted from the open to the cover of vegetation.

These studies are of enormous interest in the present context, as they provide direct experimental evidence of behavioral changes induced by the presence of predators in the wild. However, they provide only indirect evidence concerning the behavioral strategies adopted by prey species as they alter their foraging patterns. That is, animals may mechanistically move from an open location to one affording protection from aerial predation or they may do so while also increasing vigilance behaviors, with obvious additional effects on foraging efficiency. Consequently, in view of the abovementioned difficulties, a number of species were wild trapped and examined under laboratory conditions. As with studies involving laboratory animals, wild-trapped species were placed in a box containing a small burrow and exposed to 3 min of voice, 2 min of owl or control stimuli, followed by 5 min of silence. It is of interest to note that of the four species examined, only three measurably reacted to the owl call. That is, voles (*Microtus socialis*—seed and green vegetation eating, small-eared, small-eyed burrow dwelling rodents) dormice (*Eliomys melanurus*—seed-, insect-, and snail-eating, large-eared, large-eyed rodents inhabiting rocky, arid zones) and jerboa (*Jaculus jaculus*—seed- and green vegetation-eating, large-eyed, large-eared, bipedal rodents that forage over wide areas), all reacted strongly to the call of an owl. By contrast, spiny mice (*Acomys dimidiatus*—insect- and snail-eating, with moderate-sized ears and eyes and spiny fur, inhabiting rocky areas) do not appear to react (26).

To describe these findings in more detail, dormice show an increased interest in the burrow and reduce the distance they travel from it, while jerboa crouch and freeze. Data from the study involving voles are presented in Fig. 5 and show that these animals reduce their rearing behavior and significantly increase crouching and time spent in the burrow during the period of silence. These reactions contrast with behaviors expressed by laboratory mice under similar conditions and serve to graphically illustrate the differences in defensive strategies adopted by these two species. That is, voles hide in a burrow when faced with a threat, while mice attempt to escape. In this context, it is noteworthy that although reactivity to owl calls could be demonstrated in a number of species, it could not be examined in wild-trapped mice (*Mus musculus*), as they showed hyperreactivity to the test situation, characterized by explosive jumping and intense escape responses, which was independent of the stimulus presented.

That each species behaves differently is of importance for the assertion that the reactions of one species may be used to predict the responses in another. Although it may be argued that each of these behaviors are functionally equivalent, this is untenable when it may be demonstrated that various species adopt completely different strategies. That is, voles, and partially dormice, opt for the use of strategically defensible locations, jerboa display strategies designed to reduce the probability of detection (i.e., crouching, which masks their light colored ventral surface, and freezing, which reduces movement cues), and mice exhibit protean behavior. Interestingly, these strategies have clear parallels with the description of defensive behavior along the lines of the [D^3H], and suggest that different species might have different baseline starting points along this axis, with the more reactive species interpreting a particular stimulus as representing a more intense threat.

It is also of interest again to note that the expression of these strategies is modifiable by pharmaceutical intervention. Under the influence of antipanic agents, laboratory mice express organized defensive behavior (the strategy adopted by voles) in response to an owl call, rather than the protean behavior seen in control animals (25). As such, although voles have been shown to be reactive to anxiolytics in exploration models (23), it would be of extreme interest to examine the effects of drugs on the behavior of a species, which, by preference, shows organized defensive patterns under these test conditions.

In this context, the lack of reaction of spiny mice to owl calls is also worthy of further investigation. At least two possibility exist to explain this. First, the spines in the dorsal surface of these mice may serve to dissuade predators from attacking them. However, given the opportunity, Tawny owls will eat spiny mice in preference to voles (Eilam and Hendrie, unpublished observations). Alternatively, as spiny mice inhabit rocky areas and feed on snails that live on the underside of or amongst rocks, it is entirely possible that these mice are so rarely exposed to the possibility of predatory attack from the air that stimuli indicating the presence of an owl are simply irrelevant to them. That is, although owls will eat spiny mice given the opportunity, the behavioral strategies adopted by these mice in the wild makes the chances of this happening very rare. A third explanation is that these animals may be reacting to the owl call, but that this is not measurable by behavioral observation. To examine this possibility further, studies are currently underway to determine the corticosterone response of these animals and other species that do show behavioral changes. Nonetheless, the identification of a species that does not demonstrate defensive reactions in response to stimuli indicating the presence of a predator potentially enabled the relative importance of the fear of intra- or interspecific interactions for the motivation to behave in exploration models of anxiety to be examined. However, these animals posses very long whiskers and, hence, somewhat perversely, the possibility exists that they were able to gain thygmotactic cues from the underside of the open arms of the elevated plus-maze. As such, the patterns of activity displayed were exactly opposite to those that may have been expected. That is, they spent the greater part of their time on this maze on the open arms and entered the closed arms only rarely (Hendrie, Weiss and Eilam, unpublished observations). Nonetheless, these data again serve to illustrate the differences in rodent defensive strategies that are only possible to observe in comparative studies.

CONCLUSIONS

The present studies reveal that attempts to interpret results derived from animal models of anxiety is not a straightfor-

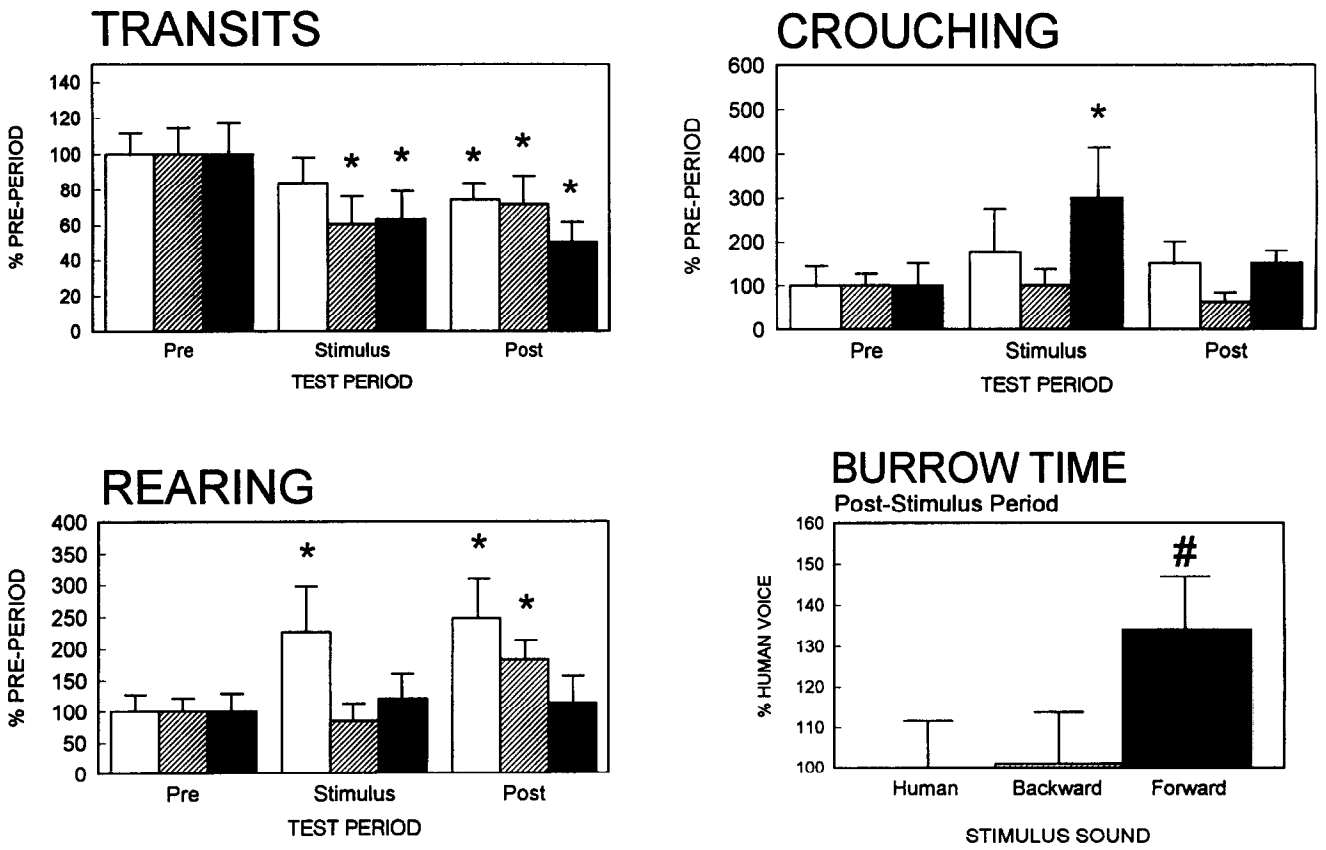

FIG. 5. The effects of Tawny owl calls on the behavior of wild trapped voles (*Microtus socialis*). Data are presented as means(±SEM) of time spent on each activity. In view of individual differences, data are expressed as a percentage of the mean time spent on each activity during exposure to the initial 3 min of exposure to human voice (pre). During the stimulus period animals were exposed to 2 min of human voice (clear bars), tawny owl call played backwards (hatched bars), or tawny owl call (blocked bars). Behavior was then assessed for a further 5 min (post). As can be seen, crouching behavior is increased during the period of tawny owl call presentation, and burrow time is also significantly increased in the postcall period. Interestingly, the increase in rearing seen in animals exposed to human voice and backward call is not seen in animals exposed to the owl call. Together, these data show that wild voles, in response to owl calls, initially crouch, then retreat into the strategically defensible burrow location, as may be expected of a heavily predated upon, burrow dwelling species. *$p < 0.05$ from prestimulus period. #$p < 0.05$ from human voice control.

ward matter. That is, for example, apparently even very simple exploration models of anxiety are open to at least two interpretations concerning the critical stimuli that activates the spontaneous fear motivating behavior in them, making unequivocal conclusions in these models impossible to reach. This is irrespective of debates concerning drug effects on motivation to explore vs. reductions in anxiety. The reason for these difficulties may possibly be because these models are considered in vacuo, without a full knowledge of the complex factors that produce the development of one characteristic vs. another. Animals have evolved to maximize their fitness in terms of food intake and reproductive success, and are additionally faced with problems relating to avoiding predation and cohabiting with members of their own and other species. The evolution of behavior is a compromize between all these factors. As such, an understanding of the organizing principles of behavior is required. An overarching theory to explain all animal behavior does not yet exist, however, one model that does have significant heuristic value is the distance-dependent defense hierarchy. The [D^{3}H] appears to allow for the generation of testable hypotheses concerning the homology of the mechanisms mediating defense at each stage of defense and human anxiety disorders. The [D^{3}H] also provides a framework within which to place animal defensive behavior and these clinical disorders. As such, by considering laboratory models in the context of the [D^{3}H] may allow for one of the aims of behavioral psychopharmacology to be potentially fulfilled. That is, to provide an insight into the relationship between animal models of anxiety and human psychological dysfunction. [For studies outlined in Figs. 1 and 2 subjects were adult male DBA/2 mice (Bantin and Kingman, Hull, UK). Animals were housed in groups of 10 (cage size 45 × 28 × 13 cm) in a temperature-controlled room (24 ± 1°C) under reversed light/dark cycle (lights off 0900 h) with food and water available ad lib for a period of at least 4 weeks prior to the start of experimentation. For studies outlined in Figs. 3 and 4, animals were held under similar conditions but were obtained from Biomedical Services, University of Leeds, UK.]

REFERENCES

1. Abramsky, Z.; Strauss, E.; Subach, A.; Kotler, B. P.; Riechman, A. The effect of Barn owls (*Tyto alba*) on the activity and microhabitat selection of *Geribillus allenbyi* and *G. pyramidum*. Oikos (in press).
2. Berry, R. J. The natural history of the house mouse. Field Stud. 3:219-262; 1970.
3. Blanchard, D. C,; Rodgers, R. J.; Hendrie, C. A.; Hori, K. 'Taming' of wild rats (*Rattus rattus*) by 5-HT_{1A} agonists buspirone and gepirone. Pharmacol. Biochem. Behav. 31:269-278; 1988.
4. Blanchard, R. J.; Blanchard, D. C. Antipredator defensive behaviours in a visible burrow system. J. Comp. Psychol. 103:70-82; 1989.
5. Blanchard, R. J.; Shepherd, J. K.; Rodgers, R. J.; Magee, L.; Blanchard, D. C. Attenuation of antipredator defensive behaviour following chronic treatment with imipramine. Psychopharmacology (Berlin) 110:245-253; 1993.
6. Boissier, J. R.; Simon, P.; Aron, C. A new method for rapid screening of minor tranquilizers in mice. Eur. J. Pharmacol. 4: 145-151; 1968.
7. Bradwejn, J.; Koszycki, D.; Couetoux du Tertre, A.; et al. The cholecystokinin hypothesis of panic and anxiety disorders: A review. J. Psychopharmacol. 6:345-351; 1992.
8. Brain, P. F. The physiology of population limitation in rodents – A review. Commun. Behav. Biol. 6:115-123; 1971.
9. Crawley, J. N. Neuropharmacologic specificity of a simple animal model for the behavioural actions of benzodiazepines. Pharmacol. Biochem. Behav. 15:695-659; 1981.
10. Davis, M. Diazepam and flurazepam: Effects on conditioned fear as measured with the potentiated startle paradigm. Psychopharmacology (Berlin) 62:1-7; 1979.
11. Dawson, G. R.; Tricklebank, M. D. Use of the elevated plus maze in the search for novel anxiolytic agents. Trends Pharmacol. Sci. 16:33-36; 1996.
12. Driver, P. M.; Humphries, D. A. Protean behaviour: The biology of unpredictability. Oxford: Oxford University Press; 1988.
13. File, S. E.; Wardill, A. G. Validity of head-dipping as a measure of exploration in a modified holeboard. Psychopharmocologia 44:53-59; 1975.
14. Gallup, G. G. Animal hypnosis: Factual status of a fictional concept. Psychol. Bull. 81:836-853; 1974.
15. Geller, I.; Bachman, E.; Seifter, J. Effects of reserpine and morphine on behaviour suppressed by punishment. Life Sci. 4:226-231; 1963.
16. Gray, J. A. The neuropsychology of anxiety. New York: Oxford University Press; 1982.
17. Green, S.; Hodges, H. Animal models of anxiety In: Willnerm, P., ed. Behavioural models in psychopharmacology: Theoretical, industrial and clinical perspectives. New York: Cambridge University Press; 1991:21-49.
18. Griebel, G.; Blanchard, D. C.; Jung, A.; Masuda, C. K.; Blanchard, R. J. 5-HT_{1A} agonists modulate mouse antipredator defensive behaviour differently from the 5-HT_{2A} antagonist pireperone. Pharmacol. Biochem. Behav. 51:235-244; 1955.
19. Haldane, J. B. S. Animal populations and their regulation. Modern Biol. 15:9-24; 1953.
20. Heinrichs, S. C.; Merlo Pich, E.; Miczek, K. A.; Britton, K. T.; Koob, G. F. Corticotropin-releasing factor antagonist reduces emotionality in socially defeated rats via direct neurotropic action. Brain Res. 581:190-197; 1992.
21. Hendrie, C. A. The calls of murine predators activate endogenous analgesia mechanisms in laboratory mice. Physiol. Behav. 49: 569-573; 1991.
22. Hendrie, C. A.; Dourish, C. T. Effects of chlolecystokinin tetrapeptide (CCK_4) and the CCK_B antagonist LY288513 in a putative model of panic in the mouse. Br. J. Pharmacol. 108:26P; 1993.
23. Hendrie, C. A.; Eilam, D.; Weiss, S. M. The effects of diazepam and buspirone on the behaviour of wild voles (*Microtus socialis*) in two models of anxiety. Psychopharmacology (Berlin) (in press).
24. Hendrie, C. A.; Neill, J. C. Exposure to the calls of predators of mice activates defensive mechanisms and inhibits consummatory behaviour in an inbred mouse strain. Neurosci. Biobehav. Rev. 15:479-482; 1991.
25. Hendrie, C. A.; Weiss, S. M. The development of an animal model of panic with predictive and face validity. In: Cooper, S. J.; Hendrie, C. A., eds. Ethology and psychopharmacology. Chichester: John Wiley; 1994:111-132.
26. Hendrie, C. A.; Weiss, S. M.; Eilam, D. Behavioural response of wild rodents to the calls of an owl: A comparative study. Anim. Behav. (in press).
27. Hogg, S.; File, S. E. Responders and nonresponders to cat odour do not differ in other tests of anxiety. Pharmacol. Biochem. Behav. 49:219-222; 1994.
28. Kavaliers, M.; Colwell, D. D. Parasite infection attenuates nonopioid mediated predator-induced analgesia in mice. Physiol. Behav. 55:505-510; 1994.
29. Kemble, E. D. Novel odors increase defensiveness and inhibit attack behaviour in mice. In: Cooper, S. J.; Hendrie, C. A., eds. Ethology and psychopharmacology. Chichester: John Wiley; 1994:191-204.
30. King, C. M. Interactions between woodland rodents and their predators. Symp. Zool. Soc. Lond. 55:219-247; 1985.
31. Klein, S. L.; Lambert, K. G.; Durr, D.; Shaeffer, T.; Waring, R. E. Influence of environmental enrichment and sex on predator stress-response in rats. Physiol. Behav. 56:291-297; 1994.
32. Kotler, B. P.; Holt, R. D. Predation and competition: The interaction of two types of species interactions. Oikos 54:256-260; 1989.
33. Lader, M. Animal models of anxiety: A clinical perspective. In: Willner, P., ed. Behavioural models in psychopharmacology: Theoretical, industrial and clinical perspectives. New York: Cambridge University Press; 1991:76-88.
34. Montgomery, K. C. The relation between fear induced by novel stimulation and exploratory behaviour. J. Comp. Physiol. Psychol. 48:254-260; 1958.
35. Price, M. V.; Waser, N. M.; Bass, T. A. Effects of moonlight on microhabitat use by desert rodents. J. Mammal. 65:353-356; 1984.
36. Ratner, S. C. Immobility in invertebrates: What can we learn? Psychol. Rev. 1:1-14; 1977.
37. Rodgers, R. J.; Cole, J. C. Anxiety enhancement in the elevated plus-maze by immediate prior exposure to social stressors. Physiol. Behav. 53:383-388; 1992.
38. Rodgers, R. J.; Cole, J. C. The elevated plus-maze: Pharmacology, methodology and ethology. In: Cooper, S. J.; Hendrie, C. A., eds. Ethology and psychopharmacology. Chichester: John Wiley and Sons; 1994:9-44.
39. Stephens, D. N.; Andrews, J. S. Screening for anxiolytic drugs. In: Willner, P., ed. Behavioural models in psychopharmacology: Theoretical, industrial and clinical perspectives. Cambridge: Cambridge University Press; 1991:50-75.
40. Treit, D.; Pinel, J. P. J.; Fibiger, H. C. Conditioned defensive burying: A new paradigm for the study of anxiolytic agents. Pharmacol. Biochem. Behav. 15:619-626; 1981.
41. Treit, D.; Menard, J.; Royan, C. Anxiogenic stimuli in the elevated plus-maze. Pharmacol. Biochem. Behav. 44:463-469; 1993.
42. Zangrossi, H.; File, S. E. Behavioural consequences in animal tests of anxiety and exploration of exposure to cat odor. Brain Res. Bull. 29:381-388; 1992.
43. Zangrossi, H.; File, S. E. Chlordiazepoxide reduces the generalized anxiety, but not the direct responses, of rats exposed to cat odor. Pharmacol. Biochem. Behav. 43:4 1195-1200; 1992.
44. Zangrossi, H.; File, S. E. Habituation and generalization of phobic responses to cat odor. Brain Res. Bull. 189-194; 1994.