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Test-Specific Effects of FG-7142 on Isolation-Induced Aggression in Mice

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RAWLEIGH, J. M. AND E. D. KEMBLE *Test-specific effects of FG-7142 on isolation-induced aggression in mice.* PHARMACOL BIOCHEM BEHAV **42**(2) 317-321, 1992—Treatment with FG-7142 decreased isolation-induced attack, but not defense, by male mice when the residents' home cages contained only a sawdust substrate. When a small wooden nesting box was added to the cage (Experiment 2), however, FG-7142 somewhat increased levels of attack. Time spent in the nesting box was also increased, while overall levels of social interaction were decreased, by drug treatment in Experiment 2. The latter findings are consistent with FG-7142's well-documented anxiogenic properties and indicate that this drug is probably proaggressive in its actions. The antiaggressive effects of FG-7142 in Experiment 1 may have resulted from drug-induced fear behaviors that were incompatible with attack. Alternatively, Experiment 2 suggests the possibility that species-typical attack may be defensively motivated under some circumstances. Although the antiagressive properties of eltoprazine and yohimbine were unaffected by the addition of the nest box (Experiment 3), the provision of some sort of refuge within the testing apparatus may be an important methodological consideration for studies employing resident-intruder paradigms.

FG-7142 Yohimbine Eltoprazine (DU 28853) Isolation-induced attack Defense Testing environment

ALTHOUGH various forms of resident-intruder tests (e.g., colony models, maternal aggression, territorial and isolation-induced aggression) have proven to be quite useful tools in identifying antiaggressive drugs (23,25,32,33), their value in characterizing the emotional/motivational processes that mediate these effects seems more problematic. Fluprazine hydrochloride (DU 27716) and related phenylpiperazines (e.g., DU 27725, 28412, 28853), for example, consistently and strongly inhibit attack behavior in a variety of these paradigms while having minimal, or no, effects on defensive behavior or social investigation (13,24-26,29), and have been characterized as serenics (5,26,27,29,30). It appears, however, that both fluprazine and DU 28853 (eltoprazine) rather strongly potentiate fearfulness in a number of experimental settings (14,21,34). The latter findings not only suggest that phenylpiperazines might be better characterized as anxiogenic rather than serenic (14,19,21), but also raises the possibility that selective reductions in attack behavior may be a rather consistent result of fear inducing treatments. Indeed, we (20) have recently shown that yohimbine, a well-characterized anxiogenic compound (6,8,10,11,15-17)), also inhibits isolation-induced attack, but not defense, in male mice. The present experiments therefore explored the effects of the benzodiazepine inverse agonist FG-7142 on isolation-induced attack. This drug produces anxiogenic effects in man (9) and animals (1,7,12,31), and is also suggested to increase timidity and inhibit aggression (35,36).

GENERAL METHOD

Subjects

Subjects were 40- to 60-day-old male CD-1 albino mice. Residents weighed 30.2-44.9 g at the time of testing, were individually housed in 38 × 20 × 25 cm glass aquaria having a sawdust substrate, and received ad lib access to Purina Rat Chow and water. The intruders weighed 0.5-5.6 g less than their respective residents and were housed in groups of six to eight.

Apparatus

Testing was conducted in the resident's aquarium and behavior was videotaped (Panasonic, WV 340P) for later scoring with the camera mounted 63 cm above the aquarium floor under 48 ft-c incandescent illumination.

Procedure

After 10-14 days of social isolation, residents were randomly assigned to weight-balanced groups, received the appropriate drug or saline treatment by interperitoneal injection, and were returned to their home cages. Thirty minutes later, an intruder was introduced into the resident's cage. Intruders received no drug treatment. The frequency and duration of

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offensive behaviors (lateral attacks and chases), defensive behaviors (box, defensive upright, immobiles, and flee), and social investigation (nose-to-nose sniffing, anogenital sniffing, and body sniffing) by residents were recorded during a 15-min encounter.

Individual measures of offensive and defensive behaviors proved to be quite variable. Chases and lateral attacks were therefore combined into an overall measure of offensive aggression. Similarly, immobile, flee, upright, and box were combined to index defensiveness and all sniffing behaviors as a measure of social investigation. To assess drug effects on overall levels of social contact, all agonistic and nonagonistic behaviors (social interaction) were also combined for further analyses. Kruskal-Wallis and/or Mann-Whitney *U*-tests were utilized to assess overall drug effects.

EXPERIMENT 1

Experiment 1 examined the effects of FG-7142 on isolation-induced aggression utilizing testing procedures quite similar to those previously used to investigate the antiaggressive effects of various phenylpiperazines and yohimbine (20,27,29,32). If there is a reasonably consistent relationship between drug-induced anxiogenesis and suppressed attack, FG-7142 might be expected to yield an antiaggressive profile.

METHOD

Subjects were 72 mice. Thirty-six mice served as residents and were designated to receive 2.5 mg/kg (low, $n = 9$) 5.0 mg/kg (medium, $n = 9$), or 10.0 mg/kg (high, $n = 10$) doses of FG-7142 or an equivalent volume of saline ($n = 8$). The remaining mice served as intruders.

RESULTS

Offensive behavior by residents is depicted in Fig. 1. Treatment with FG-7142 produced a highly significant overall suppression in the duration of attack, $H = 12.05$, $p < 0.007$. Individual comparisons revealed that all drug doses reduced attack relative to the saline group, $U = 6$–11, $p < 0.02$, but with no differences among the dose levels ($p > 0.10$). Although the frequency of attack also appeared to be decreased by FG-7142, statistical analysis failed to suggest any overall drug effect ($p > 0.10$). Although defensive behaviors tended to increase with increasing drug dosages, these behaviors were quite variable and failed to suggest a drug effect on either frequency or duration ($p > 0.10$). There was no effect of FG-7142 on frequency or duration of social investigation or total social interactions ($p > 0.10$).

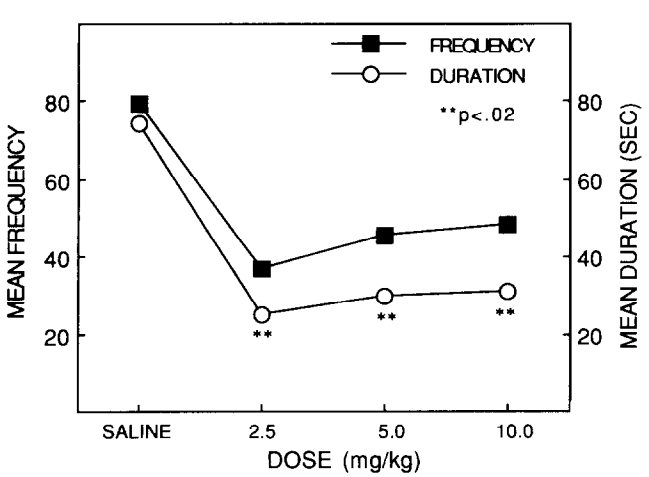

FIG. 1. Mean frequency and duration of offense by mice treated with FG-7142 or saline.

Informal observations suggested that the decreased attack duration produced by FG-7142 resulted, in part at least, from qualitative differences in offensive behaviors. Many of the lateral attacks among drug-treated mice were initiated by a lunge when intruders were at a considerable distance, were extremely brief, and were followed by rapid retreat. In addition, drugged mice sometimes engaged in defensive burying and frequently excavated small depressions in the substrate that they then entered and in which they remained immobile for brief periods of time. Such lunging attacks, defensive burying, and digging were never seen among control animals.

EXPERIMENT 2

The brief attack/retreat, defensive burying, and hole digging seen among drugged mice in Experiment 1 suggests that FG-7142 may have induced intense fear that was further exaggerated by their inability to avoid contact with intruders. If so, the effects of FG-7142 on offensive and defensive behavior may have been somewhat obscured by this testing procedure. Provision of a small nesting box to serve as a refuge might, therefore, more clearly reveal antiaggressive side effects. Indeed, the availability of a refuge or burrow system is known to significantly reduce wounding during resident-intruder encounters (22,38). Experiment 2, therefore, assessed the effects of FG-7142 on aggression when a nesting box was available in the resident's aquarium. Since suppression of offense was nearly equal at all drug does in Experiment 1, but defensive behavior seemed to be most increased at 10 mg/kg, only this dose was employed.

METHOD

Subjects were 32 experimentally naive mice. Sixteen mice served as residents and received injections of either 10 mg/kg FG-7142 (drug, $n = 8$) or saline ($n = 8$). The remaining mice served as intruders.

The apparatus and procedures for this experiment were identical to those described in Experiment 1 with one exception. A 12 × 12 × 18 cm flat grey compartment of 0.6 cm plywood having a 4.5-cm diameter opening in one wall was placed in each resident's aquarium at the beginning of social isolation.

RESULTS

As can be seen in Fig. 2, FG-7142 treatment somewhat increased, rather than decreased, overall offensive behavior. Both duration and frequency of offense were marginally elevated by drug treatment, $U(8, 8) = 15$, $p = 0.10$. Although defensive behavior also seemed to be increased, there was no reliable drug effect on either frequency or duration measures ($p > 0.10$). There was no suggestion of a drug effect on the frequency or duration of social investigation ($p > 0.10$). The drug group showed a marginally significant decrease in the duration [saline, mean = 116.5 s; drug, mean = 67.1 s; $U(8, 8) = 16$, $p = 0.10$] but not frequency ($p > 0.10$) of total social interaction. Drug treatment (mean = 268.9 s) produced a marginally significant increase in time spent in the next box over saline levels [mean = 88.1 s; $U(8, 8) = 15.5$, $p < 0.10$],

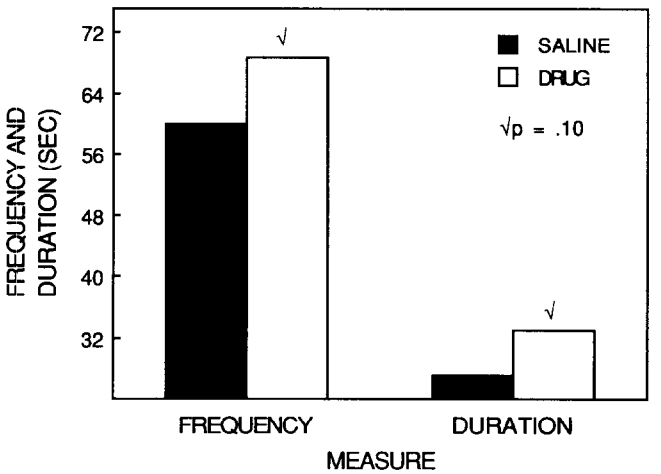

FIG. 2. Mean frequency and duration of offense by drug and saline groups.

but with no effect on number of entries ($p > 0.10$). On only one occasion did a drug-treated resident and its intruder occupy the nesting box simultaneously (duration = 1.0 s). The brief attack/retreat sequence, defensive burying, and hole digging noted among drugged mice in Experiment 1 were rarely seen in this experiment.

To further assess the effects of adding a nesting box to the resident's aquarium, the behaviors of saline and high-dose groups were compared across Experiments 1 and 2. These comparisons revealed a significant decrease in the frequency, $U(8, 8) = 12$, $p < 0.05$, and duration, $U(8, 8) = 6$, $p < 0.01$, of offensive behavior by the saline group in Experiment 2, Drug-treated mice, in contrast, significantly decreased both the frequency [Experiment 1, mean = 42.7; Experiment 2, mean = 16.2; $U(10, 8) = 15$, $p < 0.05$] and duration [Experiment 1, mean = 130.8 s; Experiment 2, mean = 12.3 s; $U(10, 8) = 8$, $p < 0.01$] of defense. There was no suggestion of a reliable change in either frequency of duration of attack behavior by the drug group or the defensive behavior of the saline group ($p > 0.10$) in Experiment 2. There was no significant change in total social interactions among control mice ($p > 0.10$) across experiments, but a highly significant decrease in its duration, $U(10, 8) = 0$, $p < 0.0004$, but not frequency ($p > 0.10$), by drug-treated mice in Experiment 2.

EXPERIMENT 3

The seemingly minor procedural change made in Experiment 2 reversed the effects of FG-7142 on aggression. Because many previous studies of putative antiaggressive drugs used procedures quite similar to those descried in Experiment 1, it seemed possible that previously reported antiaggressive effects may have been misleading as well. To explore this possibility, Experiment 3 utilized the procedures described in Experiment 2 to examine the effects of eltoprazine and yohimbine on isolation-induced aggression. Drug dosages were selected that were previously reported to inhibit isolation-induced attack (20,23,28,29) with testing procedures similar to those of Experiment 1.

METHOD

Subjects were 29 experimentally naive male resident mice designated to receive interperitoneal injections of 2.0 mg/kg yohimbine ($n = 10$), 1.0 mg/kg eltoprazine ($n = 10$), or an equivalent volume of saline ($n = 9$). An additional 29 mice served as intruders.

RESULTS

The results of this experiment are summarized in Fig. 3. Drug treatments produced a highly significant overall decrease in both the frequency, $H = 18.00$, $p = 0.0001$, and duration $H = 18.00$, $p = 0.0001$, of offense. Individual comparisons revealed that both yohimbine and eltoprazine groups differed significantly from saline in both frequency and duration of attack, $U = 0$, $p = 0.0002$, but not from each other ($p > 0.10$). There was no reliable drug effect on frequency or duration of overall defense ($p > 0.10$). There were no reliable effects of yohimbine on social investigation ($p > 0.10$). Eltoprazine, however, produced a highly significant increase in both frequency [saline, mean = 17.0; eltoprazine, mean = 58.2; $U(9, 10) = 2.5$, $p = 0.0005$] and duration [saline, mean = 49.6 s; eltoprazine, mean = 205.9 s; $U(9, 10) = 4.0$, p = 0.0008] of social investigation. Drug treatments produced a marginally significant change in frequency of entry into the next box, $H = 5.23$, $p < 0.10$, with yohimbine (mean = 4.4) somewhat decreasing and eltoprazine (mean = 11.2) somewhat increasing entrance frequency relative to saline (mean = 7.4). There were no differences in time spent in the nesting box ($p > 0.10$), however. Both yohimbine (mean = 57.7; $U = 7.0$, $p < 0.002$) and eltoprazine (mean = 70.8; $U = 12$, $p < 0.008$) produced a highly significant decrease in the frequency, but not duration ($p > 0.10$), of total social interaction when compared to saline (mean = 107.2). Simultaneous occupation of the nesting box occurred among seven mice and their respective intruders, but was nearly equally distributed among the three groups (saline = 3, yohimbine = 2, eltoprazine = 2). There were a total of 16 simultaneous entries for these subjects with a mean duration of 4.5 s.

DISCUSSION

The rather striking reversal of FG-7142 effects on isolation-induced attack in Experiment 2 clearly indicates that the presence or absence of some form of refuge may fundamentally alter conclusions about a drug's effects on aggres-

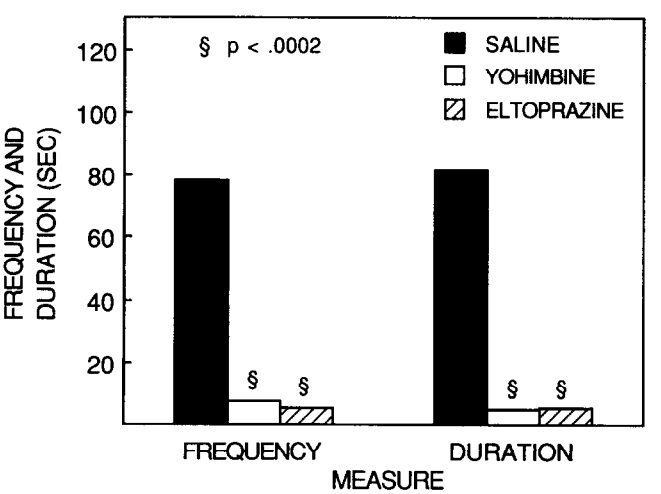

FIG. 3. Mean frequency and duration of offense by mice treated with saline, eltoprazine, or yohimbine.

sion. Indeed, Lore and coworkers (e.g., 22) emphasized that the presence of a refuge or burrow system dramatically reduces the intensity of agonistic encounters and wounding and probably more closely resembles aggressive encounters in natural settings. Consistent with the latter suggestion, the drug-treated mice in Experiment 2 not only increased time spent in the nesting box but also substantially reduced total social interactions. In contrast, total social interactions were unaffected by the drug in Experiment 1. Thus, the behavior of drug-treated mice in Experiment 2 more closely resembles the anxiogenic profile found by other authors (1,7,11,12,30). Taken together, these results suggest that the procedures employed in Experiment 2 are more ethologically relevant and characterize FG-7142's behavioral effects as proaggressive. The sharp reduction in defense among drugged mice in Experiment 2 is also quite consistent with this interpretation. Although the antiaggressive profile of eltoprazine and yohimbine were unaltered in Experiment 3, the provision of some form of refuge would nevertheless seem an important consideration of future studies of other aggression-modulating compounds. Since refuges are rather infrequently employed (13,24,25,28) in studies employing other resident-intruder paradigms (e.g., colony models, maternal aggression), their inclusion may be important in such studies as well. Although interactions occurring within such refuges may not be observable, our data suggest that joint occupancy is infrequent and brief and therefore unlikely to bias findings during short-term encounters.

The shift in FG-7142 effects on attack seen in Experiments 1 and 2 may have resulted from an active suppression of attack in Experiment 1. Drug-induced fear may have provoked the unusual lunging and digging behaviors seen in this experiment that, in turn, competed with organized attack behavior. The refuge provided in Experiment 2, then, might have allowed a sufficient reduction in fearfulness that permitted more normal attack. If so, however, it is difficult to see why the attack behavior of drugged mice in Experiment 2 did not increase over the levels of their counterparts in Experiment 1.

An intriguing alternative possibility suggested by Experiment 2 is that species-typical offensive behaviors may be defensively motivated under some circumstances. it should be noted that the aggressive behavior of drug-treated mice in Experiment 2 was topographically quite similar to that seen among saline-treated animals. Furthermore, the unusual behaviors (rapid attack-retreat, defensive burying, hole digging) noted in Experiment 1 were dramatically decreased in Experiment 2. It is therefore unlikely that the relative increase in attack by drug-treated mice in Experiment 2 was due to any qualitative change in the form of aggressive responses. The drug-induced increase in time spent in the nest box, decrease in total social interaction, and presence (though rare) of rapid attack/retreat in Experiment 2 also clearly suggest that these animals were at least somewhat fearful. These findings are consistent with a wide range of data characterizing FG-7142 as an anxiogenic (1,7,10–12,31,35,36) and suggest that the increased offense of drug-treated mice in Experiment 2 may have been fear motivated. Since yohimbine is also a well-documented anxiogenic (8,11,15,16), it might also have been expected to increase aggression in Experiment 3. Subjective reports by human subjects,however, suggest that the anxiogenic effects of FG-7142 may be considerably more potent than those of yohimbine. While yohimbine treatment is described as producing "obvious" (18) or "mild" self-reported anxiety in humans (6), FG-7142 induced an "impending fear of death or annihilation" and an inability to speak for several minutes after the onset of an anxiety attack, which in one subject led to later "verbal aggression" (9). Although these data are clearly limited and subjective, they nevertheless suggest that FG-7142 produces particularly intense fearfulness. It seems possible, therefore, that relatively modest levels of anxiety (yohimbine) may be generally antiaggressive while more intense fear (FG-7142) is proaggressive. This contrasts with the more typical finding that fear induced by pain (3,37) or by exposure to dominant conspecifics or potential predators (2,4,39) uniformly increases freezing and other fear-like behaviors and suppresses attack behavior. Finally, of course, it is also possible that the proaggressive effects of FG-7142 reflect some unusual property of this particular drug. In any case, the relationships among levels of fearfulness, situational/experimental variables, and attack behavior would seem to merit further careful examination.

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