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Effects of Eltoprazine Hydrochloride on Exploratory Behavior and Social Attraction in Mice

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KEMBLE, E. D., B. M. GIBSON AND J. M. RAWLEIGH. *Effects of eltoprazine hydrochloride on exploratory behavior and social attraction in mice.* PHARMACOL BIOCHEM BEHAV **38**(4) 759–762, 1991.—The effects of eltoprazine (DU 28853) on exploratory behavior and conspecific social attraction were examined in four experiments. Drug treatments somewhat enhanced three forms of exploratory behavior but decreased social attraction. The results indicate that eltoprazine, in sharp contrast to fluprazine, weakly ameliorates neophobic responses. Both eltoprazine and fluprazine seem to increase the aversiveness of encounters with other organisms, however. The latter effects may be mediated, in part at least, by some alteration in olfactory function.

Eltoprazine (DU 28853) Exploration Open field Maze Novel object Social attraction

THE recently synthesized compound eltoprazine hydrochloride (DU 28853) strongly inhibits attack behavior during a variety of agonistic encounters (e.g., resident-intruder and maternal aggression, muricide) while having no effect upon, or increasing, defensiveness and conspecific avoidance (19,20). Since the drug also increases social investigatory and maternal behaviors (19, 20), increased defensiveness or conspecific avoidance, when observed, is suggested to be a secondary effect of a drug-induced decrease in attack by the resident which, in turn, increases intruder aggression. This pattern of behavioral effects is strikingly similar to that seen following treatment with several other phenylpiperazine compounds such as fluprazine (DU 27716), DU 27725 and DU 28412 and has led to the characterization of this family of drugs as serenic agents [e.g., (2, 8, 17, 19, 20)].

Although there can be no doubt that various forms of agonistic encounter provide valuable tools for the detection of antiaggressive drug effects, their usefulness in revealing underlying motivational/emotional processes is more problematic. Fluprazine treatment, for example, decreases exploratory behavior and social attractiveness and prolongs reactivity to footshock (12). Such effects parallel those seen following treatment with some anxiogenic compounds and contrast with common anxiolytic effects [e.g., (3, 5, 6, 9)]. This not only suggests that fluprazine is anything but serenic in its actions but also underscores the importance of utilizing additional testing paradigms to characterize the actions of such drugs more fully. Since eltoprazine, like fluprazine, sometimes increases defensiveness and conspecific avoidance (19,20), it, therefore, seemed important to determine whether the drugs also share anxiogenic properties as well. The present experiments explore this possibility.

GENERAL METHOD

The subjects were experimentally naive CD-1 albino mice weighing 21.1–41.1 g at the time of testing. The mice were maintained on a 12-h light/dark cycle and had ad lib access to Purina Lab Chow and water throughout testing. Drug and saline treatments were administered by intraperitoneal injection 30 min prior to testing.

Since these experiments were closely similar to earlier studies of fluprazine, the apparatus and procedures will be described only briefly here. A more detailed description is available in a previous publication (12).

EXPERIMENT 1

Novel environments produce a pattern of fearful responses which wane with continued exposure (1,21). This reluctance to enter a novel environment is enhanced by fluprazine treatment (12). In addition, similar measures of exploration are inhibited by treatment with some anxiogenic drugs (5,22) and facilitated by anxiolytics [e.g., (22)]. If eltoprazine treatment enhances neophobic responses as well, then it should inhibit this form of exploration.

Method

Thirty-six weight-balanced male mice were randomly designated to receive low (1.0 mg/kg, N=9), medium (2.0 mg/kg,

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TABLE 1

MEDIAN (RANGE) ENTRANCE LATENCIES AND NUMBER OF OPEN FIELD ENTRIES

Measure	Saline	Low	Medium	High
Entrance Latency (s)	13.8 (10.0–79.1)	28.5 (13.2–112.4)	37.0 (17.9–489.4)	29.9 5.9–297.4)
Number of Entries	58 (20–87)	78* (57–118)	73 (31–90)	80† (22–158)

*$p<0.10$; †$p<0.02$.

N = 9) or high (4.0 mg/kg, N = 9) doses of eltoprazine or saline (N = 9). Immediately after injection the mice were placed in a light-proof black Plexiglas startbox which, in turn, was placed in a brightly lit open field. Thirty min later the startbox door was opened and latency to emerge into the open field and number of open field entries were recorded during a 10-min test.

Results

The results of this experiment are summarized in Table 1. Although the median entrance latencies of drug-treated mice were substantially higher than that of the Saline Group, this was due entirely to the extremely long latencies of one or two animals in each drug-treated group ($F<1.0$). Eltoprazine treatment did, however, significantly increase the number of open field entries during the test, $F(3,32)=3.20$, $p<0.05$. Multiple comparisons (Dunnett's test) revealed a marginally significant increase by the low ($p<0.10$) dose and a significant increase by the high dose ($p<0.05$). The medium dose had no significant effect, however ($p>0.10$).

EXPERIMENT 2

Although Experiment 1 suggests that eltoprazine treatment somewhat increases exploration, it is possible that drug effects were obscured by the relatively simple nature of this test and/or the high level of illumination in the open field. Experiment 2, therefore, examined the effects of the drug on exploration of a more complex maze under dim illumination.

Method

The subjects were 64 weight-balanced male mice randomly designated to receive low (N = 16), medium (N = 16) or high (N = 16) eltoprazine doses or saline (N = 16). Immediately after injection the mouse was placed in the startbox of a dimly illuminated maze which was divided into eight transverse alleyways. Alternate alleyways were divided into a cul de sac and a compartment allowing access to the next alleyway. Thirty min after placement the startbox was opened and latency to enter the maze, total time in the startbox, total compartment entries and number of entries into the two most distal compartments were recorded during a 15-min test.

Results

Analyses of variance revealed no reliable effects on entrance latencies (means = 21.0–73.0 s), time in the startbox (means = 1.8–3.5 min), startbox reentries (means = 11.4–18.1), or distal compartment entries (means = 11.8–16.2, all $Fs<1.50$). However, eltoprazine treatment produced a significant increase in total compartment entries, $F(3,60)=3.05$, $p<0.05$. Multiple comparison (Dunnett's test) revealed a marginally significant elevation of entries by the low dose (mean = 181.4, $p<0.10$), a significant elevation at the medium dose (mean = 226.2, $p<0.01$) but no reliable effect at the highest dose (mean = 173.8, $p>0.10$) when compared to saline-treated subjects (mean = 138.6).

TABLE 2

MEAN (S.D.) APPROACH AND CONTACT LATENCIES AND NUMBER OF APPROACHES AND CONTACTS TO A NOVEL OBJECT

	Latency (s)		Number	
Group	Approach	Contact	Approach	Contact
Saline	216.4 (262.8)	457.2 (263.5)	4.12 (5.30)	1.75 (3.41)
Eltoprazine	26.6* (30.5)	117.1† (88.5)	5.12 (3.76)	1.75 (1.75)

*$p<0.10$; †$p<0.005$

EXPERIMENT 3

Eltoprazine treatment seems to somewhat enhance exploration but these effects might possibly be restricted to novel environments. Experiment 3 explored the effects of eltoprazine on exploration of a novel object introduced into a familiar environment. This form of exploration is also inhibited by fluprazine (12). For this experiment only the high (4.0 mg/kg) eltoprazine dose was utilized.

METHOD

Sixteen male mice were randomly selected to receive saline (N = 8) or eltoprazine (N = 8) treatment. The subjects were individually housed in glass aquaria and tested under 28 ftc fluorescent illumination. After 5 days adaptation to the aquaria, the mice received drug or saline treatment. Thirty min later a toy plastic penguin was placed on the aquarium floor which rapidly moved its feet for 5–6 s. Latency to approach (<2.0 cm) and contact the toy and number of approaches and contacts were recorded by an experienced observer during a 10-min test.

RESULTS

All mice initially retreated from the moving toy and in some cases attempted to escape from the aquarium. These initial responses were followed by repeated approach-withdrawal behaviors which were then replaced by increasingly closer approaches as the observations continued. Table 2 summarizes the results of this experiment. Eltoprazine treatment produced a marginally significant decrease in latency to approach the novel object, $t(14)=2.03$, $p<0.10$, and a highly significant decrease in latency to contact it, $t(14)=3.47$, $p<0.005$. There was no significant drug effect on number of approaches or contacts ($ps>0.10$).

EXPERIMENT 4

Although eltoprazine decreases novelty-induced fear, its enhancement of defensiveness and conspecific avoidance during agonistic encounters (19,20) suggest that it may selectively increase the aversiveness of conspecifics in some way. If so, the drug might be expected to not only inhibit aggression but to increase avoidance of nonaggressive conspecifics as well. Interanimal distances are increased by both fluprazine (12) and yohimbine (10) treatment in a simple measure of social attractiveness. Similarly,

various anxiogenic agents decrease, while anxiolytics increase, social interactions (3, 5, 6, 9). This experiment, therefore, examined the effects of eltoprazine on social attraction between nonaggressive females.

Method

The subjects were 41 pairs of female mice randomly selected to receive low (N = 9), medium (N = 9) or high (N = 9) eltoprazine doses or saline (N = 14). Prior to testing the females were housed in groups of 8 and adapted to the testing apparatus for 20 min. No fighting was observed among these females during periodic observations and no mouse exhibited visible scarring. Thirty min after both pair members received identical drug or saline treatment, they were placed at opposite ends of a 120-cm linear runway whose floor was marked at 10-cm intervals. The distance separating the mice was recorded at 15-s intervals for 10 min and the average of these 40 observations utilized as an index of social attraction. Testing was conducted under 28 ftc fluorescent illumination.

RESULTS

Only one pair of mice (saline) exhibited any aggressive behavior and this was confined to very brief and infrequent episodes of tail rattling and lateral attack posture with no biting. Analysis of variance revealed a highly significant increase in mean interanimal distances among drug-treated groups (low, mean = 45.2 cm; medium, mean = 44.7 cm; high, mean = 40.3 cm) when compared to saline-treated animals [mean = 34.5 cm, $F(3,37) = 5.27$, $p<0.005$]. Individual comparisons (Dunnett's tests) revealed that all drug groups (low, $p<0.005$; medium, $p<0.005$; high, $p<0.05$) differed from the Control Group but not among themselves ($ps>0.10$).

DISCUSSION

The results of Experiments 1–3 indicate that eltoprazine treatment somewhat enhances exploration of novel environments and objects. The fact that these effects did not extend to all exploratory measures in any experiment and the lack of any clear dose-dependent relationship, however, suggests that these effects were weak and may have been nearly maximal at the lowest dose. Olivier and Mos (18) have provided data which is generally consistent with the latter suggestion. Utilizing several forms of conspecific agonistic encounters, they report a strong inhibition of attack by 1.0–2.5 mg/kg eltoprazine with only modest increases in effectiveness at higher (4.0–20.0 mg/kg) doses. In any case, the present pattern of mildly facilitatory effects contrasts sharply with the strong and highly consistent inhibition of exploration produced by fluprazine (12) and other anxiogenic agents (5,22). Since number of entries, but not latencies, were affected in Experiments 1 and 2, it might be suggested that eltoprazine increased exploration by inducing some degree of hyperactivity. Olivier et al. (19), however, do not note any reliable effects of the drug on activity during conspecific encounters. It is also difficult to see how this could account for the decreased approach and contact latencies seen in Experiment 3. Taken together, then, the evidence suggests that eltoprazine, unlike fluprazine, somewhat ameliorates novelty-induced fear. Thus the closely similar effects of these two drugs on conspecific attack may be mediated by at least somewhat distinct drug actions.

In contrast to its reduction of neophobic responses, eltoprazine, like fluprazine (12) or yohimbine (10), consistently increased interanimal distances. Since the simple procedure utilized in Experiment 4 seems to provide a reliable and sensitive index of gregariousness (13–15), these findings imply that eltoprazine increases the aversiveness of nonaggressive conspecifics in some way. Consistent with this suggestion, others (3, 4, 6, 9) find that anxiogenic agents decrease, while anxiolytics increase, social interactions between male rats. If eltoprazine is anxiogenic, however, the fact that it also depresses play behavior, muricide and ranacide (16,20) argues that its effects are neither restricted to conspecifics nor agonistic interactions.

Alternatively, it might be suggested that the increase in social distances noted in Experiment 4 were, in fact, a secondary effect of decreased, rather than increased, conspecific aversion. If even nonaggressive interactions are assumed to be somewhat fear-inducing, this might, in turn, suppress a tendency to explore the apparatus. If eltoprazine reduces such fear, then it could be argued that increased social distances simply resulted from a release of exploratory behavior. Since the subjects in Experiment 4, despite 20-min adaptation to the apparatus, engaged in considerable locomotor activity, this possibility cannot be excluded. Arguing against this interpretation, however, is considerable evidence that drug effects on social interactions are not secondary to increased exploration [e.g., (3)]. It also seems difficult to explain the drug's inhibition of play or predation (16,20) in this way. Taken together, then, the evidence seems to rather favor the view that eltoprazine increases the aversiveness of interactions with other organisms. Investigation of other forms of nonagonistic interactions (e.g., male-female, juvenile littermate) would be valuable in addressing this issue more fully.

Finally, the mechanism(s) by which eltoprazine alters animal interactions, however, such effects might be motivated, are of considerable interest. One intriguing clue is provided by the increases in social investigatory behaviors (among which sniffing is prominent) following eltoprazine treatment. Although such changes may be secondary to a generalized increase in the attractiveness (or decrease in the aversiveness) of conspecifics, it is also possible that some form of olfactory impairment contributes to the effect in an important way. Since olfaction is well known to be important for normal aggressive behavior [e.g., (7)], a drug-induced change in olfactory function might alter responsiveness to other organisms while leaving exploration of novel environments and inanimate objects unaffected. In this connection it should be noted that the antiaggressive effects of both fluprazine and yohimbine during paired encounters are accompanied by increased conspecific sniffing and that both drugs also alter conspecific odor preference (10,11). Since fluprazine also impairs the location of food items by olfaction its effects may also be somewhat generalized (23). Taken together, these findings clearly suggest the need for a careful examination of possible olfactory effects of eltoprazine and other antiaggressive agents as well.

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