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Acute and Subchronic Effects of Tiapride on Isolation-Induced Aggression in Male Mice

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NAVARRO, J. F. AND J. M. MANZANEQUE. *Acute and subchronic effects of tiapride on isolation-induced aggression in male mice.* PHARMACOL BIOCHEM BEHAV **58**(1) 255–259, 1997.—Although the antiaggressive properties of several atypical neuroleptics are known, the actions of tiapride (a selective dopaminergic D_2-receptor antagonist) on agonistic behavior have not been explored and there are no studies comparing acute and subchronic effects of this compound on aggression in rodents. In this work, the effects of tiapride (20–100 mg/kg, IP), administered acutely or subchronically for 10 days, on agonistic behaviour elicited by isolation in male mice were examined. Individually housed mice were exposed to anosmic "standard opponents" 30 min after drug administration, and the encounters were videotaped and evaluated using an ethologically based analysis. Tiapride decreased time spent in offenssive behaviors significantly, without an impairment of motor activity (60 and 80 mg/kg). Moreover, no tolerance to tiapride antiaggressive activity was observed after repeated administration of the drug. On the contrary, the action on immobility showed a clear tolerance development with repeated injections (100 mg/kg). The divergence found in the temporal course of tolerance to tiapride in its antiaggressive and motor effects is discussed. © 1997 Elsevier Science Inc.

Tiapride Aggression Agonistic behavior Tolerance Mice

TIAPRIDE, a substituted benzamide derivative having chemical structure similar to sulpiride and metoclopramide, acts as a selective dopamine D_2-receptor antagonist. Unlike typical neuroleptics, benzamides do not inhibit dopaminergic stimulation of adenylate cyclase activity, exhibiting a very weak affinity for D_1-receptors in ligand displacement studies. It shows preferential activity at receptors located extrastrially and has no antagonist activity at nondopaminergic receptor sites (21). In laboratory animals, tiapride displays an atypical pharmacological profile, with little propensity for causing sedation and catalepsy, although it significantly potentiates the catalepsy-inducing effect of haloperidol or chlorpromazine in rats (24). Likewise, tiapride shows antidyskinetic effects, reflecting antidopaminergic actions, particularly at sensitized receptors.

Animal and clinical studies have revealed that tiapride has anxiolytic-like properties, although the mechanism of action is uncertain. For example, Costall et al. (6) found that tiapride (0.125–40 mg/kg, SC) exhibited an anxiolytic-like profile in a simple model of anxiety ("two-compartment activity model") in mice. Similarly, Barry et al. (3) observed an increase of exploratory activity in the brightly illuminated white area of a two-compartment white/black anxiety test box, with a corresponding decrease in the black, after acute administration of tiapride (0.5–20 mg/kg, IP), indicating an anxiolytic-like action. In addition to this anxiolytic activity, from a clinical point of view, tiapride has also been shown to be effective in the treatment of tics in children (7), as well as in the management of alcohol dependence syndrome (21,25) and in the treatment of agitation, aggressiveness, and sleep disorders in elderly patients (28).

Most dopaminergic antagonists are effective antiaggressive agents. After acute treatment, all dopaminergic antagonists explored appear to share strong antiaggressive properties, but differ by the amount of motor impairment produced. Thus, whereas typical neuroleptics (like chlorpromazine, haloperidol, or spiperone) are generally considered as nonselective antiaggressive drugs (2,16,18,20), atypical neuroleptics (like clozapine, raclopride, or sulpiride) show an antiaggressive profile without markedly depressing motor activity in various animal models of aggression (1,9,11,12,23).

Although the antiaggressive properties of several atypical neuroleptics are clearly known, the effects of tiapride on ago-

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nistic behavior have not been examined and there are no studies comparing acute and subchronic effects of this compound on aggression in rodents. Therefore, the main aim of this work was to examine the effects of acute and subchronic administration of tiapride in a dose range of 20–100 mg/kg on isolation-induced aggression in male mice (29). Additionally, we also attempt to explore the presence of a possible divergence in the development of tolerance to antiaggressive and motor effects of tiapride after repeated administration, described previously with haloperidol (16,19,22).

METHODS

Subjects

Two-hundred sixty-six albino male mice of the OF.1 strain weighhing 25–30 g were obtained from "Servicio de Animales de Laboratorio," Granada, Spain. Animals arrived in the laboratory at 42 days of age and were housed under standardized lighting conditions (white lights on: 20:00–8:00), a constant temperature (21°C) and food and tap water available ad lib, except during behavioral trials.

Upon arrival in the laboratory, the subjects were allocated to two different categories. Half of the animals were housed individually in transparent plastic cages (24 × 13.5 × 13 cm) as experimental animals. The remainder were housed in groups of five to be used as "standard opponents" and were rendered anosmic temporally by intranasal lavage with 4% zinc sulphate solution (Sigma Laboratories, Madrid, Spain) on both 1 and 3 days before testing. Fighting in mice, as in most rodents, is closely related to olfaction. This type of opponent was employed because it elicits attack, but never initiates such behavior (4). Such animals rarely direct spontaneous attacks toward the test animal. Therefore, fighting is always unidirectional, and quantified easily.

All the experimental animals underwent an isolation period of 30 days before the behavioral test (isolation-induced aggression model). Social isolation is one method of increasing the level of aggressiveness in different species of animals. This phenomenon is particularly well demonstrated in laboratory mice.

Experimental Design

Eleven groups of mice were used. Individually housed animals were allocated randomly to one control group ($n = 13$) receiving physiological saline and 10 experimental groups ($n = 12$ each) receiving acute or subchronic tiapride injections. Different schedules of drug administration were employed. (a) Single-dose treatment: Each animal received saline over 9 consecutive days and tiapride on day 10. (b) Subchronic treatment: Each animal received a daily IP injection of tiapride for 10 consecutive days. (c) Saline treatment: Each animal received a daily IP injection of saline for 10 consecutive days (control group).

Drug Treatment

Tiapride (Sigma Laboratories) was diluted in physiological saline to provide appropriate doses for injections. It was administered either acutely or subchronically (for 10 days) in five doses: 20, 40, 60, 80, and 100 mg/kg. Control group received physiological saline. Drug or vehicle were injected intraperitoneally in a volume of 10 ml/kg. Aggression tests were performed 30 min after injections.

Social Encounters

After injections, an isolated animal and a "standard opponent" (marked with fur dye for identification) confronted each other in a neutral arena for 10 min. This neutral cage consisted of an all-glass area, measuring 50 × 26 × 30 cm, with a fresh sawdust substrate. While they were separated by a plastic barrier, the animals were allowed 1 min of adaptation to the neutral cage before the encounter. The social encounters were videotaped using a Sony-V8 camera. All tests were conducted under white light between the second and sixth hours of the dark phase of the artificial cycle of the animals. After each encounter, the neutral cage was washed out and the sawdust bedding was replaced.

Behavioral Analysis

The tapes were analyzed using a microprocessor and a custom-developed program (5) that facilitated estimation of time allocated to 10 broad behavioral categories. Each category included a collection of different behavioral postures and elements. The names of categorires and their constituent elements are as follows:

1. Body care (abbreviated groom, self-groom, wash, shake, scratch).
2. Digging (dig, kick dig, push dig).
3. Nonsocial exploration (explore, rear, supported rear, scan).
4. Explore from a distance (approach, attend, circle, head orient, stretched attention).
5. Social investigation (crawl over, crawl under, follow, groom, head groom, investigate, nose sniff, sniff, push past, walk around).
6. Threat (aggressive groom, sideways offensive, upright offensive, tail rattle).
7. Attack (charge, lunge, attack, chase).
8. Avoidance/flee (evade, flinch, retreat, ricochet; wheel, startle, jump, leave, wall clutch).
9. Defense/submission (upright defensive, upright submissive, sideways defensive).
10. Immobility (squat, cringe).

A detailed description of all elements can be found in Martínez et al. (13) and Brain et al. (5). This ethoexperimental procedure allows a complete quantification of the behavioral elements shown by the subject during the social encounters. Only the behavior of the isolated animals was assessed. This analysis was performed by a trained experimenter who was unaware of treatment of the groups.

Statistical Analysis

The medians for times allocated to each broad behavioral category were determined. Nonparametric Kruskal–Wallis tests were used to assess the variance of the behavioral measures over different treatment groups. Subsequently, appropriate paired comparisons were performed using Mann–Whitney *U*-tests to contrast the behavior in the different treatment groups.

RESULTS

Table 1 illustrates medians (with ranges) of accumulated times allocated to the broad categories of behavior described above. Kruskal–Wallis analysis showed that there was significant variance in the categories of threat and attack ($p < 0.001$), immobility ($p < 0.01$), body care ($p < 0.02$), and nonsocial exploration ($p < 0.01$).

Paired comparisons by Mann–Whitney *U*-tests revealed that, after acute treatment, doses of 60 ($U = 40$, $p < 0.02$), 80, and 100 mg/kg significantly reduced time allocated to threat behaviors ($U = 26$, $U = 4$, respectively, $p < 0.02$), in comparison with the saline group. Similar results were found in the behavioral category of attack, with 60 ($U = 46$, $p < 0.05$), 80, and 100 mg/kg ($U = 20$, $U = 0$, respectively, $p < 0.02$). Moreover, body care was increased by treatment, with all doses of tiapride [$U(20) = 46$; $U(40) = 33$; $U(60) = 33$; $U(80) = 43$, $p < 0.05$; and $U(100) = 17$, $p < 0.02$)]. All doses of tiapride increased nonsocial exploration behaviors, but this increase was significant ($U = 20$, $p < 0.02$) only in those animals that had received the highest dose (100 mg/kg). Immobility also increased significantly ($U = 6.5$, $p < 0.02$) in mice treated with the highest drug dose.

In comparison with the saline group, animals treated with tiapride (40, 60, 80, and 100 mg/kg) during 10 consecutive days showed significant differences in the behavioral category of threat [$U(40) = 36$; $U(60) = 39$; $U(80) = 35$; $U(100) = 28$, $p < 0.05$]. Likewise, similar findings were obtained in attack [$U(40) = 45$; $U(60) = 45$; $U(80) = 30$; $U(100) = 35$, $p < 0.05$)]. Thus, mice treated with repeated injections of tiapride significantly reduced time spent in offensive behaviors. However, no differences in these categories were observed when subchronically and acutely treated groups were compared. Body care behaviors were increased by subchronic treatment with tiapride (40 mg/kg), in comparison with the saline group ($U = 40$, $p < 0.05$). Likewise, mice treated subchronically with the highest dose of the drug (100 mg/kg) showed significantly less body care compared with mice treated acutely ($U = 24$, $p < 0.02$). When tiapride was administered for 10 days, all doses increased nonsocial exploration behaviors, but this increase was significant only in those animals that had received 40 and 100 mg/kg ($U = 29$, $U = 17$, respectively, $p < 0.02$). No differences in this category were observed when subchronically and acutely treated groups were compared. Finally, immobility increased significantly in animals treated acutely with tiapride in comparison with the subchronic-injection group ($U = 24.5$, $p < 0.02$) at 100 mg/kg dose.

There were no differences between control and experimental groups in the behavioral categories of digging, exploration from a distance, and social investigation. The median values for defense/submission and avoidance/escape were zero for all groups.

DISCUSSION

In mice, the model used most often for the study of aggression is isolation-induced fighting. As Table 1 shows, tiapride produced a clear antiaggressive effect in isolated mice treated after single-dose treatment with tiapride, reducing offensive behaviors (threat and attack) to very low levels, even abolishing attack with 80 and 100 mg/kg of the drug.

Tiapride shares its antiaggressive action with other neuroleptics. However, isolation-induced aggression in mice is not uniformly affected by all dopaminergic antagonists. While typical neuroleptics usually reduced aggression only at doses that produced pronounced sedation (2,19,20), tiapride significantly decreased aggressive behavior without affecting immobility (60 and 80 mg/kg). Therefore, these results suggest a specific antiaggressive profile of tiapride. This behavioral profile is very similar to that found with other atypical neurolep-

TABLE 1

MEDIAN VALUES (WITH RANGES) FOR TIMES (IN SECONDS) ALLOCATED TO BROAD BEHAVIORAL CATEGORIES IN ANIMALS RECEIVING ACUTE AND CHRONIC TREATMENT WITH TIAPRIDE

Behavioral categories	Doses of tiapride										
		Acute treatment					Chronic treatment				
	Saline	20 mg/kg	40 mg/kg	60 mg/kg	80 mg/kg	100 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg	80 mg/kg	100 mg/kg
Body care*	10 (2–34)	14## (7–21)	21## (8–44)	18## (4–62)	17## (0–37)	28# (3–107)	13 (5–19)	18## (5–31)	12 (1–27)	12 (5–65)	14+ (4–40)
Digging	22 (0–64)	45 (1–88)	29 (0–134)	17 (0–191)	26 (0–75)	19 (0–177)	23 (0–67)	39 (15–84)	36 (0–101)	9 (1–66)	6 (0–39)
Non social** exploration	246 (196–309)	250 (201–320)	269 (216–345)	260 (148–373)	277 (190–389)	366# (233–413)	279 (142–368)	314# (209–396)	292 (199–445)	284 (221–422)	352# (209–428)
Explore from a distance	16 (5–34)	11 (6–21)	15 (5–30)	8 (1–26)	11 (4–26)	17 (1–29)	11 (3–27)	7 (2–23)	10 (3–23)	6 (4–48)	11 (1–21)
Social investigation	89 (14–239)	143 (37–240)	83 (30–225)	115 (45–323)	156 (76–338)	116 (17–270)	98 (19–295)	118 (20–242)	106 (66–271)	150 (53–338)	148 (20–325)
Threat***	113 (59–226)	87 (48–131)	97 (42–155)	64# (1–144)	65# (3–113)	10# (0–70)	94 (7–143)	68## (16–156)	70## (9–199)	45## (3–183)	58## (1–148)
Attack***	65 (13–177)	49 (4–112)	47 (0–104)	41## (0–130)	4# (0–66)	0# (0–10.4)	60 (0–260)	22## (0–125)	22## (0–125)	23## (0–78)	11## (0–59)
Immobillity**	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–21)	8# (0–32)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–11)	0+ (0–16)

Kruskal–Wallis test showed significant variance, $*p < 0.02$; $**p < 0.01$; $***p < 0.001$.
Differs from controls on Mann-Whitney *U*-tests, $\#p < 0.02$; $\#\#p < 0.05$;
Differs from acute treatment on Mann–Whitney *U*-tests, $+p < 0.02$.

tics such as sulpiride (12,17,23), raclopride (1), and clozapine (9). Like these compounds, tiapride appears to exhibit a selective antiaggressive activity in isolated male mice. This antiaggressive effect seems to be mediated via D_2-receptors. Tiapride has no antagonist activity at nondopaminergic receptor sites (v.g., 5-HT). However, since an affinity for sigma receptors has been demonstrated for remoxipride (a benzamide), it would be noteworthy to examine the affinity of tiapride for these receptors (30).

It is interesting to emphazise that, after acute treatment of tiapride, the impairment of motor behavior, as measured by the increase found in immobility, was very small. Immobility was increased significantly by the highest dose (100 mg/kg), but only reached a median of 8 s. Moreover, other motor behaviours, such as nonsocial exploration (which represented about 50% of the total time) were also increased. These findings are in concordance with a previous behavioral study in which very high doses of tiapride were required to reduce spontaneous locomotor activity (100–275 mg/kg, orally) and induce cataleptic effects (200 mg/kg, IP) (10). Neuroleptic drugs are the most frequently used therapeutic agents in the management of violent patients. Consequently, the existence of neuroleptics that do not exert their aggression-decreasing effect at the cost of behavioral sedation has obvious clinical relevance.

Numerous pharmacological studies on aggression have focused exclusively on attacks between mice, ignoring effects of drugs on other behavioral activities occurring in aggressive mice. In this work, tiapride produced a clear increase in body care behaviors after acute treament. Morever, this effect reached significance in the five explored doses. This result is very similar to that found with other substituted benzamides, like sulpiride (11). Grooming occurs in a great variety of species. Although the neurochemistry of grooming behavior of rodents is complex, the involvement of brain dopamine systems is evident. Grooming activity is suppressed by D_2 receptor agonists (such as quinpirole) and stimulated by D_1 receptor agonists (such as SKF 38393), suggesting an oppositional model of D_1–D_2 receptor interaction in the regulation of grooming in intact rodents (8). Similarly, bilateral 6-hydroxydopamine (6-OHDA)-induced lesions of the substantia nigra produced an intense grooming activity in rats (14). A role for dopamine in the control of grooming behavior has been found not only for rodents, but also for other species (27).

Although the time spent in social investigation behaviors appears to be increased after acute tiapride treatment, the difference was not significant due perhaps to the great variation in this behavior exhibited by the mice. On the other hand, nonsocial exploration behaviors were also increased by treatment of tiapride, but reached significance only at the highest dose. The increase in these behavioral categories could be interpreted as tiapride possessing slight anxiolytic-like properties. In fact, the anxiolytic activity of tiapride has been demonstrated in several animal models (3,6), although the mechanisms responsible for this action have not been fully elucidated. The anxiolytic-like effects of 5-HT3 antagonists might raise interesting possibilities to explain the mechanisms by which benzamides produce antianxiety actions. Tiapride, however, does not show affinity for the 5-HT3 receptor (28).

With repeated treatment, no tolerance to the antiaggressive effects of tiapride was observed. Thus, as Table 1 shows, no significant differences in the categories of attack and threat were found when subchronically and acutely treated groups were compared. Moreover, with the highest dose of tiapride (100 mg/kg), tolerance to the motor effects of the compound developed, because immobility in the tiapride-treated group (used as a measurement of motor activity) was reduced progressively until reaching, after 10 days, levels approaching those of the tiapride-saline controls. In contrast with its purely motor actions, the antiaggressive effects of tiapride (100 mg/kg) persisted after subchronic treatment and no tolerance was evident.

The divergence found in the temporal course of tolerance to tiapride in its antiaggressive and motor effects is similar to that described previously with haloperidol (0.4 mg/kg) using an animal model of isolation-induced aggression in mice (19,22), suggesting that these actions are mediated through different neurophysiological mechanisms. Likewise, Mos et al. (16) recently have described a different temporal course for sedation than for the antiaggressive action of haloperidol (2 mg/kg) in the resident-intruder model of aggression in rats. On the other hand, a parellel with extrapyramidal and therapeutic effects of neuroleptics can be established. In clinical studies, it is a generally admitted fact that antipsychotic activity does not show tolerance after prolonged treatments, whereas adverse extrapyramidal side effects decrease with the passage of time. Therefore, it seems plausible to suggest that the antiaggressive action of neuroleptics in rodents might function as a model for its antipsychotic effects in humans (19,26).

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