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Behavioral Profile of Amisulpride in Agonistic Encounters Between Male Mice

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Amisulpride is a substituted benzamide derivative that acts as a selective dopamine D2/D3 receptor antagonist. Although the anti-aggressive properties of neuroleptic drugs are well known, the effects of amisulpride on agonistic interactions have not been explored, and there are no studies comparing acute and subchronic effects of this compound on aggression in rodents. In this study, we examined the action of amisulpride (5–25 mg/kg, i.p), administered acutely or subchronically for 10 days, on agonistic behavior elicited by isolation in male mice. 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. After acute treatment, amisulpride (5–20 mg/kg) exhibited an ethopharmacological profile characterized by a marked decrease of offensive behaviors (threat and attack) without an impairment of motor activity. By contrast, the anti-aggressive action of the highest dose used (25 mg/kg) was accompanied by a weak increase of immobility. Body care was also significantly enhanced after treatment with the drug (20 and 25 mg/kg), emphasizing the involvement of dopaminergic receptors in this behavior. After subchronic treatment, no tolerance to amisulpride anti-aggressive activity was observed. Overall, this behavioral profile is similar to that observed by other atypical neuroleptics. Aggr. Behav. 25:225–232, 1999. **© 1999 Wiley-Liss, Inc.**

Key words: amisulpride; neuroleptics; aggression; motor behavior; subchronic treatment; mice

INTRODUCTION

Amisulpride is one of the most recent compounds of the substituted benzamide family [Mokrim et al., 1993; Vanelle et al., 1994], being chemically related to sulpiride and sultopride [Mann et al., 1984]. Although it is clinically more potent than sulpiride, their pharmacological profiles are very similar [Mattila et al., 1996]. Likewise, this compound acts as a dopamine receptor antagonist showing a similar affinity for D2 and D3 dopaminergic receptors, and no significant interaction with D1, D4, and D5 receptors

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has been described [Boyer et al., 1995; Schoemaker et al., 1997]. Furthermore, amisulpride exhibits virtually no antagonism at nondopaminergic receptor sites. Thus, apart from a very low affinity to alpha-2 receptors, this neuroleptic drug does not antagonize other neurotransmitter receptors [Wetzel et al., 1998].

On the other hand, amisulpride displays a degree of limbic selectivity for its antidopaminergic effects [Bischoll, 1992], having been reported to possess a three-fold higher affinity for limbic structures than for striatal dopamine receptors [Bischoff et al., 1988; Scatton et al., 1995]. This characteristic could explain its apparent reduced liability for inducing extrapyramidal side effects [Perrault et al., 1997].

From a clinical point of view, amisulpride shows a versatile clinical profile, with opposite effects depending on the dose range used. At low doses it is useful for the treatment of negative symptoms of schizophrenia and dysthymia, whereas at high doses it markedly reduces positive symptoms [Paillere-Martinot, 1995]. This original bipolar pattern is probably related to the fact that low doses of amisulpride (50–150 mg/d) block preferentially D2/D3 autoreceptors, which results in an increased dopamine release [Traqui et al., 1995]. In fact, the facilitation of dopaminergic transmission at low doses due to the blockade of presynaptic D2/D3 receptors could explain the apparent antidepressive properties of this compound [Boyer et al., 1992]. On the contrary, high doses (600–1,200 mg/d) have a preferential action on postsynaptic receptors exerting an antidopaminergic effect and, consequently, a neuroleptic action [Martinot et al., 1996; Shoemaker et al., 1997].

Like other neuroleptic drugs, benzamides are usually considered to be effective anti-aggressive agents [Arregui et al., 1993; Garmendia et al., 1992; Navarro and Manzaneque, 1997; Navarro et al., 1993; Redolat et al., 1991]. In fact, the anti-aggressive properties of some substituted benzamides (such as sulpiride, raclopride, or tiapride) have been demonstrated using several animal models of aggression [e.g., Aguilar et al., 1994; Martín-López et al., 1993, 1996; Navarro and Manzaneque, 1997; Redolat et al., 1991] and also in a clinical context [Huck, 1982; Takahashi and Akagi, 1996]. However, the action of amisulpride on social encounters has not been examined, and there are no studies comparing acute and subchronic effects of this compound on aggression in rodents. Therefore, the aim of this study was to analyze the effects of acute and subchronic administration of a wide range of amisulpride (5–25 mg/kg) on agonistic interactions between male mice using an animal model of isolation-induced aggression.

MATERIALS AND METHODS

Two hundred sixty-four albino male mice of the OF.1 strain weighing 25–30 g were used. Animals were obtained from "Servicio de Animales de Laboratorio" (Granada, Spain) and arrived in the laboratory at 42 days of age. Mice were housed under standardized lighting conditions (white lights on, 20:00–8:00) at a constant temperature (21°C), and food and tap water available ad libitum, except during behavioral trials. On arrival in the laboratory, the subjects were allocated to two different categories. Half 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 temporally anosmic by intranasal lavage with 4% zinc sulfate 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. We used this

type of opponent because it elicits attack but never initiates such behavior [Brain et al., 1981]. These animals very rarely direct spontaneous attacks toward the test animals, and, consequently, fighting is always unidirectional, being easily quantified.

All the experimental animals underwent an isolation period of 30 days before the behavioral test (isolation-induced aggression model). Social isolation is an effective form of increasing the level of aggressiveness in different species of animals. This phenomenon is particularly well demonstrated in laboratory mice [Navarro, 1997; Valzelli, 1969].

Eleven groups of mice were used. Individually housed animals were allocated randomly to one control group receiving vehicle and 10 experimental groups (n=12 each) receiving acute or subchronic amisulpride injections. The schedules for drug administration consisted of the following: (1) acute treatment: each animal received vehicle for 9 consecutive days and amisulpride on day 10; (2) subchronic treatment: each animal received a daily injection of amisulpride for 10 consecutive days; and (3) vehicle: each animal received a daily injection of vehicle for 10 consecutive days (control group).

Amisulpride was diluted in a mixture of saline (93%) and ethanol (7%) to provide appropriate doses for injections. It was administered either acutely or subchronically (for 10 days) in five doses: 5, 10, 15, 20, and 25 mg/kg. The control group received vehicle (93% physiological saline and 7% ethanol). Drug and vehicle were injected intraperitoneally in a volume of 10 ml/kg.

Thirty minutes after the last injection, an isolated animal and a "standard opponent" (marked with fur dye for identification) were confronted in a neutral area for 10 min. This neutral cage consisted of an all-glass area measuring 50 × 26 × 30 cm with a fresh sawdust substrate. Before the encounter, the animals were allowed 1 min of adaptation to the neutral cage, remaining separated by means of a plastic barrier throughout this time. The social encounters were videotaped using a Sony-V8 camera. All tests were conducted under white light between the second and seventh 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.

The tapes were analyzed using a microprocessor and a custom-developed program [Brain et al., 1989; Martínez et al., 1986] that facilitated estimation of time allocated to 10 broad behavioral categories. The names of the categories 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. Exploration 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 Brain et al. [1989]. This ethoexperimental procedure allows a complete quantification of the behavioral elements shown by the subject during the agonistic encounters. Only the behavior of the isolated animal was assessed. The analysis was carried out by a trained experimenter, unaware of the treatment of the groups.

Nonparametric Kruskal-Wallis tests were used to assess the variance of the behavioral measures over different treatment groups. Subsequently, appropriate paired comparisons were carried out using Mann-Whitney U-tests.

RESULTS

Table I illustrates medians (with ranges) of accumulated times allocated to the broad categories of behavior described above. Kruskal-Wallis analysis showed that there was significance in the categories of threat, attack, body care, nonsocial exploration, social investigation, and immobility (P <.05).

Paired comparisons by Mann-Whitney U-tests revealed that, after acute treatment, amisulpride (5–25 mg/kg) significantly reduced threat andattack behaviors (P < .02) compared with the control group. This decrease in aggressive behaviors was not accompanied by a significant increase of immobility, except with the highest dose used (25 mg/kg), which provoked a weak but significant increase of this behavior compared with the control group (P < .05). Moreover, although nonsocial exploration behaviors were increased in all doses, this effect reached statistical significance only with 10 mg/kg (P < .02). Body care behaviors (20 and 25 mg/kg) and social investigation (25 mg/kg) were also increased compared with the control group (P < .05). Animals treated with amisulpride for 10 consecutive days showed significant decreases in the behavioral category of threat (5, 10, 15, and 20 mg/kg, P < .02; 25 mg/kg, P < .002). However, in the behavioral category of attack, only the doses of 5–20 mg/kg (P < .05) and 25 mg/kg (P < .02) of the drug significantly reduced these behaviors. Immobility was also significantly enhanced with 10–20 mg/kg (P < .05) and 25 mg/kg (P < .02) of amisulpride compared with the control group. Finally, nonsocial exploration and social investigation behaviors were significantly increased with 10 mg/kg (P < .02) and 20–25 mg/kg (P < .05), respectively.

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

DISCUSSION

As Table I shows, amisulpride possesses remarkable anti-aggressive properties after acute treatment, reducing offensive behaviors (threat and attack) within a wide range of doses (5–25 mg/kg). This anti-aggressive effect was not accompanied by an increase in immobility, except with the highest dose (25 mg/kg), in which a weak (median=3 s) but significant increase in these behaviors was found. Although the increased immobility observed in animals treated with the highest dose apparently suggests a nonselective anti-aggressive action of amisulpride, other behaviors with an evident motor component did not exhibit significant decreases. In fact, social investigation behaviors were significantly augmented with 25 mg/kg of the drug.

The slight motor impairment found coincides with the generalized observation that this compound produces marked motor effects in mice (e.g., catalepsy) only at higher

TABLE I. Time Allocated to Broad Behavioral Categories in Animals Receiving Acute and Subchronic Treatment With Amisulpride

		Median time, sec (range)									
		Acute amisulpride treatment					Subchronic amisulpride treatment				
Behavioral categories	Vehicle	5 mg/kg	10 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg	5 mg/kg	10 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg
Body care[a]	5 (1–13)	7 (1–31)	5 (0–25)	9 (1–21)	17[b] (1–85)	11[b] (0–23)	8 (3–28)	8 (2–27)	7 (2–70)	11 (1–32)	7 (0–16)
Digging	4 (0–25)	4 (0–35)	1 (0–24)	4 (0–41)	7 (0–61)	10 (0–54)	4 (0–28)	1 (0–38)	0 (0–32)	1 (0–12)	0 (0–11)
Nonsocial exploration[a]	335 (216–430)	374 (221–474)	409[c] (287–480)	347 (264–508)	359 (133–475)	337 (229–467)	366 (269–424)	417[c] (353–494)	361 (293–423)	364 (293–511)	394 (269–493)
Explore from a distance	10 (3–18)	10 (3–15)	13 (3–28)	13 (3–20)	10 (1–27)	10 (1–19)	9 (6–25)	12 (4–27)	9 (4–19)	8 (2–15)	8 (4–20)
Social investigation[a]	68 (21–175)	93 (43–238)	116 (18–243)	90 (50–247)	72 (39–404)	153[b] (57–230)	112 (23–276)	55 (21–152)	80 (36–259)	111[b] (51–204)	96[b] (49–212)
Threat[a]	103 (56–211)	43[c] (0–105)	50[c] (0–166)	42[c] (1–155)	52[c] (1–146)	65[c] (5–106)	60[c] (0–106)	53[c] (0–101)	57[c] (0–106)	60[c] (0–100)	27[d] (0–115)
Attack[a]	52 (1–131)	13[c] (0–235)	2[c] (0–76)	14[c] (0–52)	3[c] (0–44)	8[c] (0–47)	16[b] (0–101)	13[b] (0–84)	12[b] (0–129)	18[b] (0–71)	6[c] (0–57)
Immobility[a]	0 (0–10)	0 (0–64)	0 (0–33)	0 (0–5)	1 (0–43)	3[b] (0–15)	0 (0–38)	3[b] (0–34)	3[b] (0–71)	4[b] (0–17)	16[c,e] (0–60)

[a]Kruskal-Wallis test showed significant variance ($P < .05$).
[b]Differs from controls on Mann-Whitney U-tests ($P < .05$).
[c]Differs from controls on Mann-Whitney U-tests ($P < .02$).
[d]Differs from controls on Mann-Whitney U-tests ($P < .002$).
[e]Differs from acute treatment on Mann-Whitney U-tests ($P < .05$).

doses [Navarro et al., 1997]. In this context, the relative absence of motor impairment after amisulpride treatment has been related to its higher affinity for the D2/D3 receptors located on limbic and hippocampal structures [Bischoll, 1992; Mattila et al., 1996].

The increase in time spent in social investigation could reflect an anxiolytic action of amisulpride. In fact, increases in these exploratory behaviors have been consistently described after treatment with anxiolytic agents. Likewise, such a behavioral category has been commonly used to assess the anxiety-changing properties of drugs [Brain et al., 1991; Rodgers, 1997]. Our findings are in concordance with those of other studies using benzamides with demonstrated anxiolytic properties, such as sulpiride [Martín-López et al., 1993] or tiapride [Navarro and Manzaneque, 1997]. On the other hand, the possible anxiolytic action in mice is in agreement with the therapeutic clinical profile of the drug [Mann et al., 1984].

It is interesting to note that body care behaviors were also significantly increased with amisulpride (20 and 25 mg/kg). Although the neurochemistry of grooming behavior is complex, the involvement of dopaminergic receptors is widely accepted. The increase in this behavioral category found in our experiment may be explained on the basis of the anti-D2 profile of amisulpride [Scatton et al., 1995; Sokoloff et al., 1992]. In fact, it has already been reported that grooming activity is stimulated by D2 receptor antagonists and also by D1 receptor agonists, suggesting an oppositional model of D1-D2 receptor interaction in the regulation of grooming in intact rodents [Eilam et al., 1992]. Moreover, our results are similar to those found with other drugs with high selectivity as antagonist of central dopaminergic D2 receptors, such as sulpiride [Martín-López et al., 1996] or tiapride [Navarro et al., 1996].

With repeated treatment, no tolerance to the anti-aggressive effects of the drug developed. Thus, as Table I shows, no significant differences in the categories of attack and threat were found when subchronically and acutely treated groups were compared. An absence of tolerance to anti-aggressive effects has been also described with other neuroleptics, such as haloperidol [Navarro et al., 1993; Puigcerver et al., 1996], tiapride [Navarro and Manzaneque, 1997], or zuclopenthixol [Manzaneque and Navarro, 1999].

After repeated administration of amisulpride for 10 consecutive days, a significant increase in immobility was observed, especially at the highest dose used. Therefore, the effect of amisulpride on immobility was more marked after subchronic treatment. This unexpected action might reflect an accumulation of the drug over time. Another possible explanation for this phenomenon could be an accumulation of active metabolites. However, amisulpride has few metabolites, and they all seem to be inactive [Dufour and Desanti, 1988].

In summary, mice acutely treated with amisulpride exhibited an ethopharmacological profile characterized by a selective decrease of offensive behaviors (5–20 mg/kg) without an impairment in motility, except with the highest dose employed (25 mg/kg), in which a weak increase in immobility was observed. After subchronic treatment with the drug, no tolerance to amisulpride anti-aggressive activity was found.

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