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D_2-Like Dopamine Receptor Mediation of Social-Emotional Reactivity in a Mouse Model of Anxiety: Strain and Experience Effects

Paul L. Gendreau, Ph.D., John M. Petitto, M.D., Jean-Louis Gariépy, Ph.D., and Mark H. Lewis, Ph.D.

We examined the effects of the D_2-like dopamine receptor agonist quinpirole on social-emotional reactivity in two inbred mouse strains. An important objective of this study was to determine whether these effects could be modulated by differential housing conditions (i.e., isolation versus group housing). Moreover, as motor activity is an important control for the assessment of drug effects on emotional behavior, the effects of quinpirole were tested in two inbred mouse strains (A/J and C57BL/6J) low and high in motor activity, respectively. Levels of emotional reactivity were assessed in response to mild social stimulation provided by a nonaggressive conspecific. Quinpirole increased stationary forms of reactivity (i.e., startle, kicking, defensive posture, vocalization) in both isolated and group-housed A/J mice. This effect was more pronounced and observed at lower doses in isolated than in group-housed A/J mice. Quinpirole also induced jump behavior in isolated but not group-housed A/J mice. The shift to the left in the dose-response curve of quinpirole in isolated A/J mice indicated that D_2-like dopamine receptor functions can be altered by social experience. Quinpirole only marginally increased stationary and locomotor reactivity (i.e., jump) in isolated C57BL/6J mice, whereas it markedly reduced motor activity in group-housed mice of this strain. The investigation of emotional reactivity within a social context and using strains that differ in motor activity permitted the effects of drugs on emotional reactivity to be dissociated from the effects on motor activity. Given that social-emotional reactivity was elicited by what typically should have been mild and nonthreatening stimuli, this model may be highly relevant to understanding the neurobiology of anxiety. Finally, these data support an important role for dopamine in the mediation of social-emotional reactivity.
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Fear refers to a constellation of motor-behavioral, physiological, endocrinological, and neurochemical patterns that may be produced in response to threatening and potentially harmful situations. Although fear generally constitutes a normal and adaptive emotional response designed to protect the individual from pain and injury, excessive, persistent, or unrealistic fear (e.g., panic, phobia) may have important detrimental consequences upon the individual's health and social-emotional development (Kagan et al. 1988). The study of fear and related constructs (e.g., anxiety, emotionality) has relied on various rodent models (for a review, see File 1987; Lister 1990). These models generally consist of an animal's response to bright or open space (e.g., open field, elevated plus-maze, light-dark transition test) or to stimuli that have been associated with pain or discomfort (e.g., fear-potentiated startle, Geller-Seifter

From the Department of Psychology (PLG, JLG), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and the Department of Psychiatry (PLG, JMP, MHL), University of Florida, Gainesville, Florida.

Address correspondence to: Dr. P.L. Gendreau, Department of Psychiatry, University of Florida, College of Medicine, P.O. Box 100256, Gainesville, FL 32610-0256.

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conflict test). Fear assessment has also been conducted within contexts involving a predator (Blanchard et al. 1993; Griebel et al. 1995) or an aggressive conspecific (Puglisi-Allegra and Cabib 1988). Compared with solitary test situations that typically induce a limited set of behavioral responses (e.g., defecation, freezing), social situations involving a predator or a conspecific can generate a wider variety of defensive or fear-mediated behaviors such as escape, upright and sideways defensive postures, vocalization, freezing, and social withdrawal. Thus, social contexts or paradigms may be particularly useful for the investigation of drug effects on specific behavioral patterns associated with fear or anxiety.

Studies of the neurochemical mechanisms underlying the behavioral and physiological patterns related to fear and anxiety have indicated a variety of neuromodulators interacting at various levels in the central nervous system. Particular attention has been given to the benzodiazepine, noradrenergic, and serotonergic systems, which have been shown to modulate fear and anxiety in a variety of test situations (File 1996; Shephard 1986). In contrast, little attention has been directed toward the dopaminergic system. This is somewhat surprising given that dopamine is known to mediate the motor, endocrine, and cognitive responses associated with stressful or aversive stimuli (LeMoal and Simon 1991; Salamone 1994). Dopamine has also been found to regulate certain psychiatric disorders associated with social-emotional disturbances (Carlsson 1988; Seeman 1994; Waddington 1993). Furthermore, similar to the effects of benzodiazepines and other well-established anxiolytic compounds, the D_2-like receptor antagonist sulpiride was found to reduce anxiety-like activity in various solitary test situations, including the light-dark transition test (Costall et al. 1987; Pich and Samanin 1986), the elevated-plus maze (Rodgers et al. 1994), and the conflict test as well (Pich and Saminin 1986). Sulpiride also decreased defensive behavior in mice confronted with an aggressive conspecific (Puglisi-Allegra and Cabib 1988). Conversely, the prototypical D_2 agonist quinpirole has been reported to increase defensiveness in mice interacting with an unfamiliar and nonaggressive conspecific (Cabib and Puglisi-Allegra 1989; Gao and Cutler 1993; Puglisi-Allegra and Cabib 1988). Quinpirole, however, was found ineffective in inducing anxiety in the elevated plus-maze (Rodgers et al. 1994), suggesting a specific role for D_2-like dopamine receptors in mediating fear or anxiety-like response to social stimuli.

Fear expression and the effects of dopaminergic compounds on these behavioral measures can be altered significantly by varying the level of environmental stimulation provided during development. For instance, animals that have been socially isolated are generally more fearful than animals reared in groups. This outcome has been documented in a variety of situations and animal species, including fish (Davis 1975), chicks (Jones and Waddington 1992), ducks (Melzack et al. 1959), mice (Gendreau et al. 1997; Kršiak 1975), rats (Wright et al. 1990), dogs (Melzack 1969), as well as nonhuman primates (Mason and Green 1962; Suomi 1987). Evidence has now accumulated indicating that social isolation produces alterations in dopaminergic function. When compared to group-housed animals, isolated animals have been characterized by enhanced sensitivity to the stereotypic and motor effects of d-amphetamine and apomorphine (Ahmed et al. 1995; Guisado et al. 1980; Jones et al. 1990, 1992; Lewis et al. 1990; Sahakian et al. 1975; Wilmot et al. 1984, 1986). The effects of d-amphetamine on acoustic startle response have also been found to be greater in isolated animals (Kokkinidis and MacNeill 1982). To what extent activation of D_1-like vs. D_2-like dopamine receptors contributes to the enhanced behavioral effects of mixed dopamine agonists in isolated animals has not yet been established. As D_1/D_2 interactions are required for the expression of a number of behaviors (Carlson et al. 1987; Waddington and Daly 1993), evidence indicates that both D_1-like (Gariépy et al. 1998, in press; Lewis et al. 1994) and D_2-like dopamine receptor functions (Guisado et al. 1980) can be altered by isolation housing.

The parameters of the test situation and rearing conditions are not the only determining factors for the expression of fear and for the effects of drugs on its behavioral correlates. Significant variations in fear response (Rex et al. 1996; Shanks and Anisman 1988; Trullas and Skolnick 1993) and in the effects of dopaminergic compounds on emotional (Cabib and Puglisi-Allegra 1989; Gendreau et al. 1997; Nikulina and Klimek 1993) and motor behavior (Fink and Reis 1981; Seale et al. 1984; Skrinskaya et al. 1992) have been found among rat and mouse strains. In this regard, we found that drugs acting selectively at the D_1 receptor subtype primarily altered the expression of locomotor forms of social-emotional reactivity (e.g., escape and jump) in high-motor activity C57BL/6J mice, whereas it had little effect in low-motor activity A/J mice (Gendreau et al. 1997). In this strain, however, social-emotional reactivity was increased by dihydrexidine, a dopamine agonist showing only a 10-fold selectivity for D_1 versus D_2-like receptors, suggesting a potential role for the D_2 receptor subtype in mediating emotional reactivity in A/J mice.

The present study was therefore designed to examine the effects of the D_2-like dopamine receptor agonist quinpirole on social-emotional behavior in A/J and C57BL/6J mice that have been reared in social isolation or in groups. Previous studies have shown that quinpirole significantly increased escape, defensive posture, freezing while decreasing social investigation in group-housed C57BL/6 mice exposed to an unfamiliar conspecific (Cabib and Puglisi-Allegra 1989; Puglisi-Allegra and Cabib 1988). It was hypothesized that isolation housing

would result in a shift to the left in the dose-response curve for quinpirole, the effects of the dopamine agonist expected to be greater in mice reared in isolation than in mice reared in groups. Furthermore, as suggested by our previous findings, quinpirole was expected to be particularly effective in inducing social-emotional reactivity in A/J mice.

MATERIALS AND METHODS

Animals

Mice from the A (n = 56) and C57BL/6 (n = 40) strains (Jackson Laboratories, Bar Harbor, ME) that were to be isolated arrived in our facilities at 21 days of age. The day after, mice were individually housed in clear plastic cages (29 × 18 × 13 cm) for 5 weeks. Six-week-old group-housed mice of the A (n = 18) and C57BL/6 (n = 17) strains were obtained from the same vendor 2 weeks before testing. Animals were kept in groups of four or five. All animals had access to food and water ad libitum and were kept on a 12:12-h light-dark cycle in a temperature-controlled room (23°C). Animals were left undisturbed in their home cage except for cage and bedding replacement. Group housed, untreated C3H/HeNH mice (Sprague Dawley, IN) of similar age and weight were used as social partners. This strain was selected, as our previous studies have shown these mice to provide adequate levels of social stimulation without being aggressive. Each partner was used approximately twice for testing but never on the same day.

Social Interaction Test

After injection, mice were returned to their home cage for 10 min. The test mouse was then confined to one-half of a Plexiglas chamber (21 × 30 × 30 cm) while a group-housed, untreated C3H/HeNH partner mouse was placed into the other half of the chamber. A metal panel that prevented the animals from being in contact was removed after a 5-min acclimation period. The social interactions were coded for 5 min by an observer who was unaware of assignment to housing and drug conditions and who had attained a high level of reliability with other certified observers in previous experiments (Gariépy et al. 1995; Lewis et al. 1994). Behavioral categories included vocalization, kicking, startle, defensive posture (upright and sideways), jump, escape, social investigation, and aggression (i.e., fight, bite, feint, and aggressive grooming). In addition, the intensity of escape behavior was determined by counting the number of times the subject crossed the midline of the testing chamber during an escape behavior (until the next social contact or within a 5-s period after the social contact). This measure has been shown to be a sensitive index in assessing strain and drugs effects on escape behavior (Gendreau et al. 1997). Testing was conducted in a dimly illuminated room within the first 4 h of the dark cycle. All aspects of the present study were conducted within NIH guidelines for animal research and were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida.

Drug

Quinpirole [(-) trans (4aR,8aR)-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo [3,4-g] quinoline HCl] was dissolved in a 0.1% solution of ascorbic acid. Mice were administered 0, 3.0, or 6.0 mg/kg. Given that isolation was expected to produce a shift to the left in the dose-response curve, an additional dose of 1.0 mg/kg was given to isolated mice only. Injections were made subcutaneously 15 min before testing (including the 5-min acclimation period). Raclopride [(S)-3,5-dichloro-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6methoxy-benzamide L-tartrate] was dissolved in distilled water and injected (5.0 mg/kg) subcutaneously 15 min before quinpirole administration. Both drugs were injected in a volume of 4 to 8 ml/kg body weight.

Statistical Analyses

As in previous studies, all behavioral categories except social investigation were expressed as frequency per number of interactions to control for strain differences in the number of contacts with the partner mouse as well as for variations in the number of social contacts attributed to housing and drug conditions. Social investigation was expressed as total frequency over the whole test. Strain and housing effects were analyzed in vehicle-treated mice using a 2 (strains) × 2 (housing conditions) ANOVA. The effects of quinpirole were analyzed separately in isolated and group-housed mice with a 2 (strains) × 4 (doses, 0, 1.0, 3.0, 6.0 mg/kg) and a 2 (strains) × 3 (doses, 0, 3.0, 6.0 mg/kg) ANOVAs, respectively, followed if necessary by Duncan multiple range tests.

RESULTS

Strain and Housing Differences in Social-Emotional Behavior

Strain and housing differences in social-emotional reactivity were assessed by analyzing the behavior of vehicle-treated mice. Significant main effects for strain were obtained for several categories. Specifically, low-locomotor activity A/J mice were significantly more likely to freeze ($F(1, 28) = 21.11$, $p < .001$), startle ($F(1, 28) = 5.72$, $p < .05$), and kick ($F(1, 28) = 8.49$, $p < .01$) in response to social contact than C57BL/6J mice. Conversely, high-locomotor activity C57BL/6J mice showed

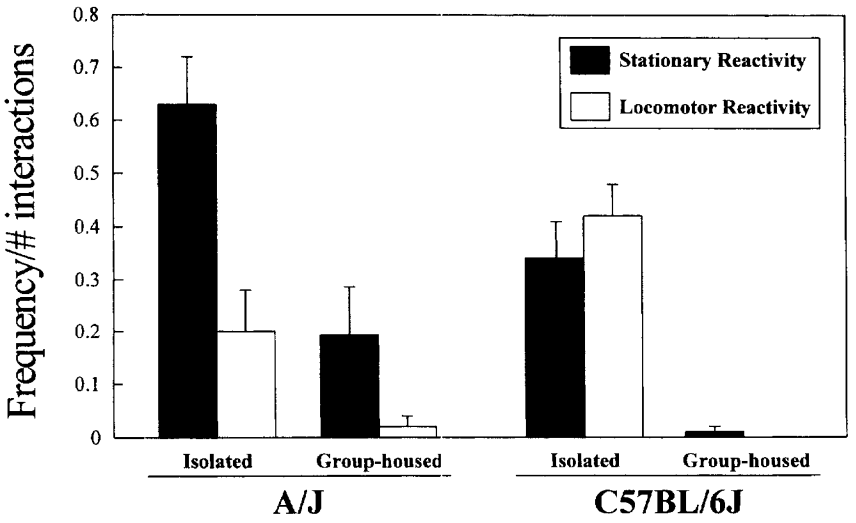

Figure 1. Strain differences and effects of isolation housing on stationary (i.e., startle, kicking, vocalization, defensive posture, and freezing) and locomotor (i.e., jump and escape) reactivity in A/J and C57BL/6J mice (mean and SEM).

a greater tendency to escape from the partner mouse than did A/J mice. This difference was significant regarding the intensity of escape, that is, the number of times the subject crossed the midline of the chamber while escaping away from the conspecific (F (1, 28) = 3.42, p = .075). Figure 1 summarizes the strain differences in stationary reactivity (i.e., freezing, kicking, startle, defensive posture, vocalization) versus locomotor reactivity (i.e., jump, escape). C57BL/6J mice also displayed more aggressive behavior (F (1, 28) = 7.53, $p < .01$) and more nonagonistic social investigation (F (1, 28) = 26.78, $p < .0001$) than A/J mice.

Significant main effects of housing on social-emotional reactivity were also found. As shown in Figure 1, levels of social-emotional reactivity were quite low in group-reared A/J and C57BL/6J mice injected with vehicle. Analysis of individual behaviors indicated that isolation housing increased defensive posture (F (1, 28) = 6.48, $p < .05$), kicking (F (1, 28) = 11.09, $p < .01$), aggressive behavior (F (1, 28) = 4.52, $p < .05$), and the frequency (F (1, 28) = 16.86, $p < .001$) as well as the intensity (F (1, 28) = 31.50, $p < .0001$) of escape behavior. Some of these effects were strain specific, however, as demonstrated by significant strain by condition interactions. The increase in kicking after isolation housing was observed in A/J mice only (F (1, 28) = 5.09, $p < .05$), whereas the intensity of isolation-induced escape was greater in C57BL/6J mice (F (1, 28) = 6.86, $p < .05$). Finally, only isolated C57BL/6J mice showed aggressive behavior (F (1, 28) = 4.52, $p < .05$).

Effects of Quinpirole on Social-Emotional Behavior in Isolated Mice

Quinpirole markedly increased stationary reactivity in isolated mice (F (3, 72) = 6.35, $p < .001$). As shown in Figure 2, the effects of quinpirole on stationary reactivity in isolated animals were substantially more pronounced in A/J mice than in C57BL/6J mice. Although the strain by drug interaction was only marginally sig-

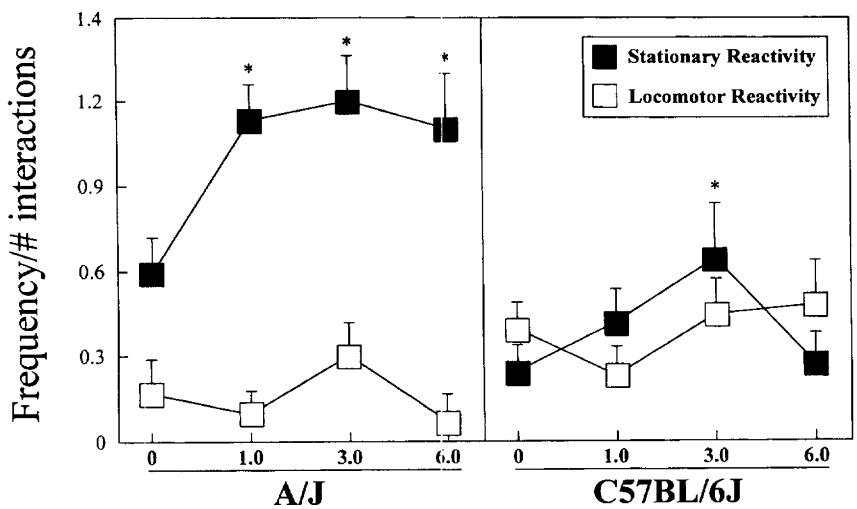

Figure 2. Effects of quinpirole on stationary (startle, kicking, vocalization, defensive posture, and freezing), and locomotor (jump and escape) reactivity in isolated A/J and C57BL/6J mice (mean and SEM); * $p < .05$.

Table 1. Effects of Quinpirole (mg/kg) on Social-Emotional Behaviors in Isolated and Group-Housed A/J Mice

	Isolated				Group-Housed		
Behavior	**0**	**1.0**	**3.0**	**6.0**	**0**	**3.0**	**6.0**
Startle	0.08 ± 0.03	0.04 ± 0.02	0.14 ± 0.03	0.20 ± 0.09	0.01 ± 0.01	0.04 ± 0.02	0.16 ± 0.04[a]
Kicking	0.20 ± 0.05	0.78 ± 0.09[a]	0.30 ± 0.10	0.39 ± 0.11	0.00 ± 0.00	0.03 ± 0.02	0.17 ± 0.06[a]
Vocalization	0.02 ± 0.01	0.06 ± 0.04	0.17 ± 0.08	0.06 ± 0.04	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.02
Defensive posture	0.12 ± 0.05	0.13 ± 0.04	0.47 ± 0.10[a]	0.36 ± 0.07[a]	0.06 ± 0.05	0.06 ± 0.04	0.31 ± 0.07[a]
Freezing	0.21 ± 0.05	0.16 ± 0.04	0.15 ± 0.06	0.13 ± 0.04	0.12 ± 0.06	0.07 ± 0.04	0.11 ± 0.05
Jump	0.00 ± 0.00	0.00 ± 0.00	0.10 ± 0.04[a]	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Escape	0.20 ± 0.08	0.13 ± 0.04	0.33 ± 0.10	0.10 ± 0.05	0.02 ± 0.02	0.02 ± 0.01	0.04 ± 0.03
Aggression	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Social investigation	4.9 ± 1.3	0.2 ± 0.1[a]	0.1 ± 0.1[a]	0.2 ± 0.1[a]	2.3 ± 1.0	0.5 ± 0.3[a]	0.0 ± 0.0[a]

Note: Results are expressed as number of occurrences/total interactions (mean and SEM), except for social investigation which represents total frequency for the whole test.
[a]Different from 0 mg/kg ($p < 0.05$).

nificant (F (3, 72) = 2.23, $p = .092$), separate analyses conducted for each strain indicated that stationary reactivity was increased at all doses in A/J mice, whereas C57BL/6J mice showed a slight, but significant, increase only at the 3.0 mg/kg dose ($p < .05$). Quinpirole significantly increased kicking (F (3, 72) = 9.16, $p < .001$), defensive posture (F (3, 72) = 6.44, $p < .001$), and vocalization (F (3, 72) = 3.33, $p < .05$) in isolated mice. A marginal effect was also found for startle (F (3, 72) = 2.38, $p < .077$). Significant strains by drug interactions were found for kicking (F (3, 72) = 5.73, $p < .001$) and defensive posture (F (3, 72) = 6.44, $p < .001$). Post hoc comparisons revealed that quinpirole increased these behaviors in A/J mice only, the increases being significant at 1.0 mg/kg for kicking and at 3.0 and 6.0 mg/kg for defensive posture ($p < .05$). None of the specific behaviors subsumed under the category of stationary reactivity was significantly altered by quinpirole in C57BL/6J mice.

Quinpirole also altered the expression of locomotor reactivity in isolated mice as indicated by a marginal drug main effect (F (3, 72) = 2.54, $p = .063$). The two behaviors categorized as locomotor reactivity, namely escape and jump, were differentially affected by the D_2-like agonist. Quinpirole had no effect on the frequency of escape behavior in isolated mice but decreased the intensity at 1.0 mg/kg (F (3, 72) = 4.94, $p < .01$). In contrast, jump was increased (F (3, 72) = 5.46, $p < .01$). There was a significant strain by drug interaction for this behavior (F (3, 72) = 4.46, $p < .01$), indicating that the increase in jump was significant at 3.0 mg/kg in isolated A/J mice and 6.0 mg/kg in isolated C57BL/6J mice ($p < .05$). Finally, no aggression was observed in isolated C57BL/6J mice administered quinpirole as revealed by the significant strain by drug interaction (F (3, 72) = 7.75, $p < .001$). Social investigation was also reduced in both strains (F (3, 72) = 37.55, $p < .0001$), an effect that was more pronounced in C57BL/6J mice (F (3, 72) = 5.61, $p < .01$) given their higher levels under vehicle condition. The mean and standard error of the mean for each behavior are indicated in Table 1 (A/J mice) and Table 2 (C57BL/6J).

In an independent experiment using isolated A/J mice, we found that pretreatment with the D_2-like receptor

Table 2. Effects of Quinpirole (mg/kg) on Social-Emotional Behaviors in Isolated and Group-Housed C57BL/6J Mice

	Isolated				Group-Housed		
Behavior	**0**	**1.0**	**3.0**	**6.0**	**0**	**3.0**	**6.0**
Startle	0.01 ± 0.00	0.01 ± 0.01	0.06 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Kicking	0.04 ± 0.02	0.09 ± 0.03	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Vocalization	0.11 ± 0.05	0.02 ± 0.01	0.18 ± 0.08	0.03 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Defensive posture	0.17 ± 0.04	0.28 ± 0.05	0.31 ± 0.06	0.22 ± 0.05	0.00 ± 0.00	0.11 ± 0.05	0.06 ± 0.05
Freezing	0.01 ± 0.01	0.05 ± 0.01	0.12 ± 0.07	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00
Jump	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.02	0.09 ± 0.03[a]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Escape	0.42 ± 0.08	0.28 ± 0.08	0.48 ± 0.09	0.51 ± 0.13	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Aggression	0.11 ± 0.04	0.00 ± 0.00[a]	0.00 ± 0.00[a]	0.00 ± 0.00[a]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Social investigation	11.5 ± 1.6	0.5 ± 0.2[a]	0.6 ± 0.3[a]	1.6 ± 1.3[a]	13.8 ± 2.3	1.5 ± 1.0[a]	0.6 ± 0.4[a]

Note: Results are expressed as number of occurrences/total interactions (mean and SEM), except for social investigation which represents total frequency for the whole test.
[a]Different from 0 mg/kg ($p < 0.05$).

Table 3. Effects of Raclopride Pretreatment on Quinpirole-Induced Social-Emotional Reactivity in Isolated A/J Mice

Behavior	Vehicle + Quinpirole (3 mg/kg)	Raclopride (5 mg/kg) + Quinpirole (3 mg/kg)
Startle	0.17 ± 0.04	0.11 ± 0.04
Kicking	0.25 ± 0.06	0.15 ± 0.06
Vocalization	0.01 ± 0.01	0.00 ± 0.00
Defensive posture	0.24 ± 0.06	0.01 ± 0.01[a]
Freezing	0.15 ± 0.02	0.34 ± 0.04[a]
Jump	0.01 ± 0.01	0.00 ± 0.00
Escape	0.07 ± 0.02	0.00 ± 0.00[a]
Aggression	0.00 ± 0.00	0.00 ± 0.00
Social investigation	0.13 ± 0.13	0.50 ± 0.27

Note: Results are expressed as number of occurrences/total interactions (mean and SEM), except for social investigation which represents total frequency for the whole test.
[a]Different from vehicle + quinpirole ($p < 0.05$)

antagonist raclopride (5 mg/kg) blocked the effects of quinpirole (3.0 mg/kg) on defensive posture ($F(1, 15) = 13.94$, $p < .01$) and prevented the expression of escape ($F(1, 15) = 12.56$, $p < .01$). This was paralleled by a substantial increase in freezing behavior ($F(1, 15) = 14.61$, $p < .01$). The results are indicated in Table 3.

Effects of Quinpirole on Social-Emotional Behavior in Group-Housed Mice

Quinpirole also increased social-emotional reactivity in mice that had been reared in groups, but as depicted in Figure 3, these effects were observed exclusively in A/J mice and only at the highest dose ($p < .05$). As indicated by the significant strain by drug interaction, quinpirole increased stationary reactivity in group-housed A/J mice ($F(2, 29) = 16.90$, $p < .0001$). Specifically, quinpirole increased startle ($F(2, 29) = 11.83$, $p < .0001$), kicking ($F(2, 29) = 6.25$, $p < .01$), vocalization ($F(2, 29) = 3.75$, $p < .05$) and defensive posture ($F(2, 29) = 4.75$, $p < .05$) in these mice (see Table 1). The only effect of quinpirole in group-housed C57BL/6J mice was a substantial reduction in social investigation ($F(2, 29) = 14.43$, $p < .0001$), which reflected a marked decrease in motor activity in this strain.

DISCUSSION

We examined the effects of the D_2-like dopamine receptor agonist quinpirole on social-emotional reactivity in two inbred mouse strains. One important objective of this study was to determine whether these effects could be modulated by social experience. It was hypothesized that mice reared in social isolation would be more sensitive to quinpirole treatment and would show enhanced social-emotional reactivity when compared with mice reared in groups. Furthermore, as motor activity may be an important control for the assessment of

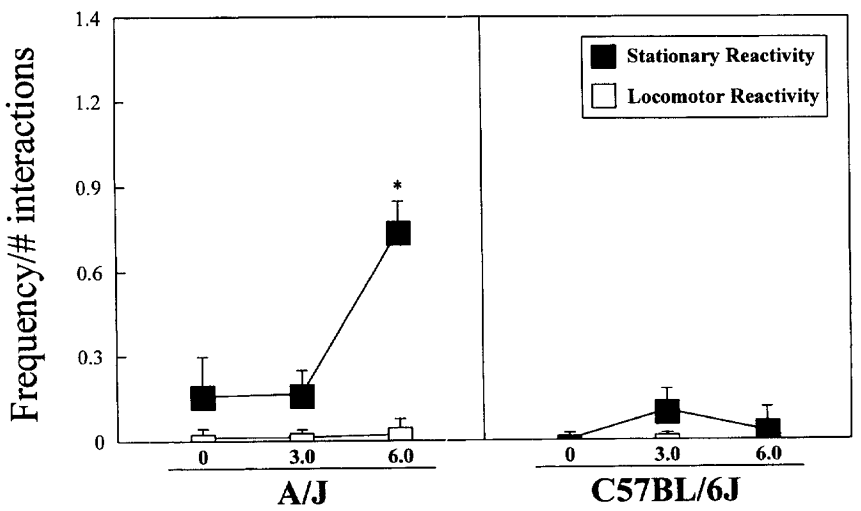

Figure 3. Effects of quinpirole on stationary (startle, kicking, vocalization, defensive posture, and freezing) and locomotor (jump and escape) reactivity in group-housed A/J and C57BL/6J mice (mean and SEM); * $p < .05$.

drug effects on emotional behavior, the effects of quinpirole were tested in low (A/J) and high (C57BL/6J) locomotor activity mice. Based on previous results (Gendreau et al. 1997), the effects of quinpirole were expected to be strain specific, modulating stationary forms of reactivity (e.g., freezing, defensive posture, startle, kicking) in A/J mice and locomotor forms of reactivity (e.g., escape, jump) in C57BL/6J mice.

The present results in drug-naive mice are consistent with our previous findings as isolated A/J mice exhibited freezing, startle, and kicking, whereas isolated C57BL/6J mice showed escape and aggressive behavior. In addition, as previously observed, levels of social-emotional reactivity were very low in vehicle-treated group-housed mice of both strains.

Quinpirole produced a substantial increase in stationary reactivity in isolated A/J mice, increasing startle, kicking, vocalization, and defensive posture. Quinpirole also increased jump behavior in these mice. In contrast, the D_2-like dopamine agonist only marginally enhanced locomotor reactivity (i.e., jump) in isolated C57BL/6J mice. Interestingly, opposite effects have been previously observed with the selective D_1 agonist SKF-81297, which substantially increased locomotor reactivity (i.e., escape and jump) in isolated C57BL/6J mice while having only minimal effects in isolated A/J mice. In addition, the selective D_1 antagonist SCH-23390 altered the expression of social-emotional reactivity in isolated C57BL/6J mice but had no effect in isolated A/J mice (Gendreau et al. 1997). On the other hand, the dopamine agonist dihydrexidine, which has only a 10-fold selectivity for D_1 over D_2 receptors (Darney et al. 1991), increased reactivity in both strains. The present findings with quinpirole support the hypothesis that the effects of dihydrexidine on social-emotional reactivity in A/J mice were the result of D_2-like receptor activation. These results thus indicate a strain-specific role for D_1-like and D_2-like dopamine receptors in mediating isolation-induced social-emotional reactivity.

Quinpirole also increased stationary forms of reactivity (i.e., startle, kicking, and defensive posture) in group-based A/J mice. This effect was less pronounced than in isolated A/J mice and was observed at the highest dose only. Similar to the present findings in A/J mice, dopamine agonist-induced social-emotional reactivity was also observed at lower doses and at higher rates in isolated Institute for Cancer Research (ICR) mice than in group-housed ICR mice (Lewis et al. 1994). Other studies have demonstrated that isolated animals were more sensitive to the motor stimulant effects of apomorphine (Sahakian et al. 1975; Wilmot et al. 1984, 1986), amphetamine (Ahmed et al. 1995; Jones et al. 1990; Lewis et al. 1990; Sahakian et al. 1975; Wilmot et al. 1984, 1986), and cocaine (Phillips et al. 1994) than animals reared in groups. The effects of amphetamine on acoustic startle have been also shown to be more pronounced in isolated rats (Kokkinidis and MacNeill 1982). The shift to the left in the dose-response curve of quinpirole in isolated A/J mice suggests that isolation altered dopamine receptor function. This adaptive mechanism may involve upregulation of dopamine receptors (Gariépy et al. 1995, in press; Guisado et al. 1980) and/or enhanced sensitivity to dopamine (Oehler et al. 1987) and may take place at postsynaptic and/or presynaptic sites (Jones et al. 1992). The dopaminergic systems thus appear to be highly sensitive to experiential input and may contribute to the heightened emotional reactivity typically observed in isolated animals (Gariépy et al. 1996).

It has been reported previously that quinpirole substantially increased levels of social-emotional reactivity in group-housed C57BL/6 mice (Cabib and Puglisi-Allegra 1989; Puglisi-Allegra and Cabib 1988). Specifically, in group-housed C57BL/6 mice exposed to a non-aggressive, untreated male mouse of the same strain, quinpirole was found to increase the duration of escape and defensive posture, and to decrease social investigation. This was shown over a wide dose range from 0.1 to 5 mg/kg. In the present study, however, quinpirole at both doses tested (3 and 6 mg/kg) had no specific effect on social-emotional reactivity but markedly reduced motor activity in group-housed C57BL/6J mice. Similar motor depressant effects have been reported for quinpirole in this strain at doses up to 32 mg/kg (Middaugh et al. 1996; Shannon et al. 1991).

The contradictory results concerning the effects of quinpirole in group-housed C57BL/6J mice are difficult to reconcile, although some methodological differences exist between the studies. For one, mice were 3 to 4 weeks younger in our study. Not only have the effects of dopaminergic ligands on motor behavior been found to be age dependent (Van Hartesveldt et al. 1994) but the expression of social behavior has been also shown to change over ontogeny, with an increasing probability of aggression from either the subject or the mouse partner as the animals grow older (Cairns et al. 1985). Importantly, in this study, C3H/HeNH mice served as partners, whereas C57BL/6 mice were used in the other studies (Cabib and Puglisi-Allegra 1989; Puglisi-Allegra and Cabib 1988). It is probable that C57BL/6 mice, serving as partners, initiated more social contact and were more aggressive, thus providing more overall stimulation than the moderately active and less aggressive C3H/HeNH mice. Also in the present study, both the subject and the partner were equally habituated to the testing chamber, whereas in the other studies only the subject was habituated, creating a "resident-intruder" situation more likely to induce agonistic interchanges. More intense and possibly more threatening stimulation increases the probability that emotional behavior will be displayed, especially once the central pathways associated with these behaviors have been activated by dopamine agonists.

The present results indicate important strain differences in the effects of quinpirole on social-emotional reactivity. As A/J mice were more sensitive to the stimulant effects of quinpirole, prior reports indicated that A/J mice were also more sensitive than C57BL/6J mice to the convulsant effects of the inverse benzodiazepine receptor agonist β-CCM (Mathis et al. 1994). Conversely, diazepam increased light-dark transitions in C57BL/6J mice but not in A/J mice (Mathis et al. 1994, 1995). A/J and C57BL/6J mice also exhibit important differences in the expression of motor-emotional behavior. A/J mice are less active (Messeri et al. 1972) and performed less light-dark transitions (Mathis et al. 1994, 1995) than C57BL/6J mice, suggesting that A/J mice are more "emotional" than C57BL/6J mice. Both strains, however, exhibited preference for the closed arms of the elevated plus-maze (Trullas and Skolnick 1993). Thus, both genetic and contextual factors can influence the expression of emotional behavior as well as the effects of drugs on these behaviors.

It has been reported that C57BL/6Cr mice (Charles River Laboratories) have higher D_2-like receptor densities in lateral striatum (35%) and the accumbens (38%) versus A/J mice, with no difference in the substantia nigra, pars compacta, or the ventral tegmental area (Kanes et al. 1993). As microinfusion of quinpirole to the nucleus accumbens induces hypolocomotion (Mogenson and Wu 1991; Van Hartesveldt et al. 1992), differences in D_2-like receptor functions in this brain area may be, at least in part, responsible for the depressant effects of quinpirole on motor behavior in C57BL/6J mice. On the other hand, the increase in social-emotional behavior after quinpirole administration may involve D_2-like receptors located in the amygdala, a structure having important dopaminergic connections with the olfactory tubercle and nucleus accumbens (Amaral et al. 1992; Louilot et al. 1985). The central nucleus of the amygdala contains a relatively high number of D_2-like dopamine receptors (Murray et al. 1994; Scibilia et al. 1992) and has been shown to mediate fear-related responding, more particularly conditioned freezing behavior (Davis et al. 1994; Le Doux et al. 1988). Lesions of the amygdala have been found to reduce conditioned and unconditioned freezing (Blanchard and Blanchard 1972; Kim et al. 1993; Maier et al. 1993). Conversely, electrical or pharmacological stimulation of the amygdala has been found to induce escape (Hilton and Zbrozyna 1963; Ursin and Kaada 1960), rage reaction (Reis and Gunne 1965), and aggressive behavior (Adamec 1990).

The present findings suggest that dopamine plays an important modulatory role in the expression of social-emotional reactivity. As seen in the present study, a wide variety of behavioral responses including freezing, startle, defensive posture, vocalization, kicking, escape, and attack can be produced in response to social stimuli. As pointed out previously (Gendreau et al. 1997), activation of the dopaminergic system increases the probability that lower motor forms of emotional reactivity (e.g., freezing, startle, kicking) would be replaced by higher motor forms of reactivity (e.g., escape, jump). It has been shown previously that D_1-like receptor activation dose-dependently increased escape and jump behavior in isolated C57BL/6J mice, whereas blockade of this receptor subtype increased freezing and kicking (Gendreau et al. 1997). Similarly, as shown in the present study, quinpirole increased kicking at a lower dose (1 mg/kg) and jump at a higher dose (3 mg/kg) in isolated A/J mice. Quinpirole did not affect the frequency of freezing, however, but a lower dose of the D_2-like dopamine agonist could have been effective in increasing this form of reactivity. In the present study, freezing behavior was defined as a reduction in overt motor behavior during mild contact or investigation by the conspecific. It was characterized by an abnormally rigid posture and was typically accompanied by the flattening of the ears, the closing of the eyes, and occasionally by crouching. Dopaminergic systems have been hypothesized to play an indirect role on freezing by regulating flight systems (Blackburn et al. 1992). By reducing motor function, low doses of D_2-like dopamine agonists therefore increase the probability that freezing may be displayed. Similar effects have been obtained with administration of dopamine antagonist (Blackburn and Phillips 1990; Gendreau et al. 1997). In the present study, pretreatment with raclopride increased freezing and abolished escape in isolated A/J mice, an effect likely due to the D_2-like dopamine antagonist alone. Although higher doses of dopamine agonists are expected to induce higher motor forms of reactivity, replacing freezing and other stationary forms of reactivity, quinpirole up to 6 mg/kg, did not reduce freezing in isolated A/J mice. Similar observations have been made in mice characterized by high levels of social freezing (Gariépy et al. 1995; Lewis et al. 1994). These results indicate a certain independence between flight and freezing systems.

In isolated C57BL/6J mice, administration of quinpirole prevented the expression of aggressive behavior. As with freezing, dopamine likely plays an indirect role in aggression. Indeed, suppression of aggressive behavior has been observed with dopaminergic ligands at doses that either facilitated or depressed overt motor-emotional behavior (Baggio and Ferrari 1980; McMillen et al. 1989; Miczek et al. 1994). Whereas the serotonergic system has been linked more directly to the expression of aggressive behavior (Bell and Hobson 1994; Sanchez et al. 1993; Valzelli and Bernasconi 1979), the dopaminergic system appears to be critical in conditioned avoidance behavior (Blackburn et al. 1992) as well as in avoidance behavior elicited by novel stimuli (Bardo et al. 1996; Hooks and Kalivas 1995). Consistent with this hypothesis, quinpirole markedly reduced social investi-

gation in isolated and group-housed mice of both strains. Similar observations have been reported with selective D_1 and D_3 dopamine agonists at doses that either increased or reduced overt behavioral activation (Gariépy et al. 1995; Gendreau et al. 1995, 1997; Lewis et al. 1994).

In this regard, it is interesting to note that although quinpirole decreased motor activity in C57BL/6J mice, no increase in freezing or decrease in the frequency of escape was observed. In addition, quinpirole induced jump behavior. These findings confirm other reports indicating that the motor depressant effects induced by D_2-like dopamine agonists can be overcome by increasing the levels of external stimulation (e.g., electrical shock), which results in an enhanced emotional response (Franklin and Tang 1995; Blackburn and Phillips 1990; Blackburn et al. 1992). An important feature of the present study is that emotional reactivity was not associated with painful or aversive experience (e.g., shock, repeated defeat) and was not generated by clearly threatening stimuli (e.g., predator, aggressive conspecific). Instead, the threshold for emotional responding was lowered by social isolation and high levels of emotion reactivity were induced by mild social contact provided by an unfamiliar and nonaggressive male mouse. As these animals exhibit an exaggerated emotional responding to what typically should be nonthreatening social stimuli, this model may be more exemplary of anxiety than fear and may be highly relevant to understanding the neurobiology of anxiety-related behaviors (Parker and Morinan 1986).

Although quinpirole has been reported to have significant affinity for D_3 dopamine receptors (Gehlert et al. 1992; Sokoloff et al. 1990), a receptor subtype largely localized to limbic structures (Bouthenet et al. 1991; Schwartz et al. 1993), there has been so far no consensus regarding the selectivity of quinpirole for D_3 over D_2 dopamine receptors. Previous studies in isolated C57BL/6J mice, however, have shown that the putative D_3 dopamine agonists 7-OH-DPAT and PD128907 markedly increased stationary reactivity at low doses and locomotor reactivity at higher doses (Gendreau et al. 1995). These results suggest a different profile for quinpirole and the two D_3 dopamine agonists in mediating social-emotional reactivity in C57BL/6J mice. Similar conclusions have been reached regarding the effects of quinpirole and 7-OH-DPAT on cross-sensitization to apomorphine and cocaine in Wistar rats (Mattingly et al. 1993, 1996).

In concert with other findings in various mouse strains (Cabib and Puglisi-Allegra 1989; Gao and Cutler 1993; Gariépy et al. 1995; Lewis et al. 1994) and in nonhuman primates as well (Crowley et al. 1974; Schlemmer and Davis 1981), the present results thus indicate an important role for dopamine system in modulating anxiety-like responses to social stimuli. Anxiogenic properties have also been reported for the D_2-like agonist RU-24926 (Simon et al. 1993) and the dopamine uptake inhibitors amphetamine and GBR 12783 (Shimada et al. 1995; Simon et al. 1993, 1994) in nonsocial test conditions (e.g., elevated plus-maze, light-dark transition test), whereas the D_2-like receptor antagonist sulpiride had anxiolytic-like effects in these tests (Costall et al. 1987; Pich and Samanin 1986; Rodgers et al. 1994).

Several studies, however, have failed to demonstrate the anxiogenic effects of dopamine agonists (Hjorth et al. 1986, 1987; Rodgers et al. 1994, 1996) or the anxiolytic effects of dopamine antagonists (Cole and Rodgers 1994; Shimada et al. 1995) in nonsocial test conditions. As demonstrated in this study, the effects of drugs on emotional behavior are influenced by genetic and experiential factors as well, making generalization between strains, species, and housing conditions, problematic. In addition, the propensity to be "emotional" in a nonsocial context has been shown to be a poor predictor of the level of emotional reactivity exhibited in response to social stimulation (Berton et al. 1997; Gariépy et al. 1988). Accordingly, great care must be also exercised in generalizing drug effects on emotional behavior elicited by nonsocial versus social stimuli.

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