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Behavioural Brain Research 114 (2000) 107–117

BEHAVIOURAL BRAIN RESEARCH

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Research report

D_3 and D_2 dopamine receptor agonists differentially modulate isolation-induced social-emotional reactivity in mice

Paul L. Gendreau [a], John M. Petitto [a], Andreana Petrova [a], Jean-Louis Gariépy [b], Mark H. Lewis [a,*]

[a] *Brain Institute, Department of Psychiatry, University of Florida, P.O. Box 100256, Gainesville, FL 32610-0256, USA*
[b] *Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3270, USA*

Received 6 December 1999; received in revised form 21 March 2000; accepted 21 March 2000

Abstract

Following isolation housing, mice typically exhibit heightened emotional reactivity to mild social stimulation. Aggression, social avoidance and a variety of defensive behaviors that differ in terms of motor activation (e.g. freezing, escape) can be observed depending on strain. Previous studies suggested that D_2-like dopamine (DA) receptors play an important, albeit strain specific, role in the mediation of particular forms of defensive behavior. D_3 receptors are subtypes of D_2-like receptors that are highly expressed in limbic areas of the brain and, therefore, they have been hypothesized to mediate emotional behavior. This study examined the effects of the putative D_3 receptor agonists 7-OH-DPAT and PD128907 on social-emotional behavior in isolated C57BL/6J and A/J mice. These effects were compared with those of the selective D_2 receptor agonist PNU91356A. All three DA agonists increased non-locomotor forms of defensive behavior (e.g. freezing, upright defensive posture). These effects were observed at low doses in C57BL/6J and at higher doses in A/J mice. Only the D_3 receptor agonists were effective in increasing locomotor forms of defensive behavior (i.e. escape, jump) at higher doses. These effects were more pronounced in C57BL/6J mice than A/J mice. The increases in stationary and locomotor defensive behavior were accompanied by marked reduction in social investigation in both the strains. Aggressive behavior was also abolished in the aggressive C57BL/6J strain. These results support previous findings and suggest that DA agonists potentiate defensive behavior and/or social fearfulness. They also suggest that D_3 and D_2 DA receptors differentially modulate the expression of social-emotional reactivity and indicate the importance of strain in examining the effects of DA ligands on emotional behavior. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Dopamine; D_3 receptors; Emotional behavior; Social behavior; Defensive behavior; Anxiety; Fear

1. Introduction

Social isolation induces a complex set of neurobehavioral abnormalities that has been referred to as the 'social deprivation syndrome' in non-human primates [29] and 'the isolation syndrome' in rats [34] and mice [82]. A typical and prominent characteristic of animals that have experienced social isolation, is the heightened behavioral reactivity they exhibit to what would normally be mild and non-threatening stimulation. This has been shown in a variety of animals, including fish [14], chicks [35], mice [11,20,25], dogs [49] and non-human primates [46,50,76]. This isolation-induced alteration in behavior is particularly conspicuous within social contexts involving an unfamiliar conspecific [24,61]. In non-human primates for instance, social isolation induced social avoidance [29,47,81] and/or aggressiveness [33]. Despite relying on different experimental procedures (e.g. onset and duration of the isolation period), similar outcomes have been observed in mice. Indeed, isolation housing has been reported to reduce social investigation [12,78] and to increase aggressive behavior [11,39,87]. A variety of other behavioral elements (e.g. freezing, upright defensive posture,

* Corresponding author. Tel.: +1-352-2940415; fax: +1-352-3922579.
E-mail address: mlewis@psych.med.ufl.edu (M.H. Lewis).

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PII: S0166-4328(00)00193-5

kicking, vocalization, jump, escape) that have been referred to as defensive behavior [7,58], flight [30] or timidity [38] have also been observed in isolated mice.

The specific behavioral effects of social isolation have been demonstrated to be dependent upon strain. A/J mice for instance, have been shown to mainly exhibit freezing and kicking and no aggression in response to social contact, whereas C57BL/6J mice have been characterized by high levels of escape and aggressive behavior [24,25,71,72]. Since different emotional behaviors probably result from interactive but specific neuropharmacological mechanisms [7], the use of social context and the use of two mouse strains having different behavioral propensities, provide an opportunity to investigate the behavioral specificity of drug effects. In addition, the use of animals that show certain levels of emotional reactivity under vehicle conditions is important to examine the possibility that a drug has anxiolytic-like effects. On the other hand, extreme levels of emotional reactivity under vehicle conditions may conceal the anxiogenic-like effects of a drug. In this regard, the social isolation paradigm offers an opportunity to examine both pharmacological effects.

Dopamine (DA) plays an important role in mediating the effects of isolation housing on the social behavior of mice. Amphetamine and other dopaminergic drugs increased escape behavior and reduced aggression in isolated Swiss-Webster mice [51]. Anti-aggressive effects in this strain have also been reported with the D_2-like DA receptor agonist quinpirole [79]. In isolated ICR mice, administration of the D_1/D_2 DA receptor agonist dihydrexidine induced escape and social avoidance while decreasing aggressive behavior [22,21,43]. Similar effects were observed in isolated C57BL/6J mice with dihydrexidine and the selective D_1 receptor agonist SKF-81297 [24]. However, these agonists did not affect the social-emotional behavior of the isolated A/J mice. Conversely, we found that quinpirole substantially increased defensive behavior (e.g. upright defensive posture, startle, kicking) in A/J mice, whereas it had only marginal effects in C57BL/6J mice [25]. These results indicate important strain differences in the effects of D_1-like and D_2-like DA agonists on isolation-induced social-emotional reactivity.

In recent years, considerable attention has been focused on the potential role of D_3 DA receptors in modulating emotional dysfunction [66,69,73]. Steiner et al. [75] reported that D_3 DA receptor knockout mice had reduced 'anxiety-like' activity in the open field and elevated plus-maze, suggesting that D_3 receptors may modulate emotional behavior. In another study in mice, however, the putative D_3 receptor agonist 7-OH-DPAT had no specific effects on 'anxiety-like' activity in the elevated plus-maze, but rather, reduced all motor behaviors [62]. Similar effects were observed with quinpirole [63]. However, few empirical data have related the D_3 receptor subtype to the mediation of social-emotional behavior. Kagaya et al. [36] showed that putative D_3 receptor agonists reduced huddling in rats. In another study, D_3 receptor agonists were reported to reduce ultrasonic vocalization in rats [5]. These reductions were observed at low doses, suggesting that D_3 DA autoreceptors may have an anxiolytic-like function in this paradigm.

To our knowledge, no data are currently available on the effects of selective D_2 and D_3 DA agonists on isolation-induced social-emotional reactivity. As mentioned above, the D_2-like DA receptor agonist quinpirole was found to increase the defensive behavior in isolated A/J mice, whereas it had little effect on isolated C57BL/6J mice [25]. Other studies with different strains of mice and with different paradigms have also reported an increase in defensive behavior after quinpirole administration [10,19]. Although quinpirole was initially reported to be over 100-fold selective for D_3 versus D_2 receptors [73], more recent evidence indicates that its selectivity for D_3 receptors may be rather low [4,31,45,59,77]. More selective pharmacological tools are now available to examine the role played by D_3 and D_2 DA receptors in mediating behavior. These include 7-OH-DPAT and PD 128907, which have been shown to exhibit a 7–20- and a 18–54-fold in vitro affinity for D_3 over D_2 receptors, respectively [28,31,45,59]. In this study, we examined the effects of these two putative D_3 receptor agonists on social-emotional reactivity in isolated A/J and C57BL/6J mice. These effects were compared with those of PNU 91356A, a DA agonist having a 50-fold selectivity for D_2 over D_3 receptors [57].

2. Materials and methods

2.1. Animals

Male mice (21-day-old) of the A/J and C57BL/6J strains were obtained from Jackson Laboratories (Bar Harbor, ME). At 22 days of age, mice were individually housed in clear plastic cages ($29 \times 18 \times 13$ cm) for 5 weeks. Six-week-old male C3H/HeNHsd mice were purchased 2 weeks prior to testing from Harlan (Indianapolis, IN) and used as partners for the social interaction test. C3H/HeNHsd mice were housed in groups. They were chosen as partners, as earlier studies have shown them to provide mild social contact at a reasonably high rate. Mice were kept on a 12-h light/dark cycle (lights off at 18:00 h) in a temperature controlled room (23°C). Food and tap water were always available.

2.2. Drug

R(±)-2-dipropylamino-7-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (7-OH-DPAT), PD 128907 [(*S*+)-(4aR,10bR)-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano-[4,3-b]-1,4-oxazin-9-ol hydrochloride] and PNU 91356A ((*R*)-5,6-dihydro-5-(propylamino)4H-imidazo[4,5,1-ij]quinolin-2-(1H)-one monohydrochloride] were dissolved in ascorbic acid (0.1%). 7-OH-DPAT (0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg), PD 128907 (0.1, 0.3, 1.0 or 3.0 mg/kg), PNU 91356A (0.03, 0.1, 0.3, 1.0, 3.0 or 10.0 mg/kg) and vehicle solution were administered subcutaneously. As in previous studies, all agonists were injected 15 min prior to the social interaction test. All the compounds were injected in a volume of 4 ml/kg body weight. PNU 91356A was a generous gift from Pharmacia and Upjohn (Kalamazoo, MI). 7-OH-DPAT and PD 128907 were purchased from Research Biochemicals (Natick, MA). Dose ranges were selected based on previous studies in mice ([59,74], Kjell Svensson, pers. commun.).

2.3. Social interaction test

As in the earlier studies [24,25], the test mouse (8-week-old) was confined to one half of a $21 \times 30 \times 30$ cm Plexiglas chamber 10 min following injection, while a group-housed, untreated C3H/HeNHsd male mouse of approximately the same age and weight was placed into the other half of the chamber. A removable panel located in the middle of the chamber prevented the animals from being in contact with each other. The panel was removed after 5 min and the social interactions between the subject and the partner were recorded for an additional 5 min. The behavioral coding system used for this purpose was established in previous studies [11,23,56] and included the behaviors of both the test and partner mice. All the observations were coded by an observer who was unaware of the drug conditions and who had attained a high level of reliability with other observers in previous experiments [21,22,43]. Testing was conducted in a dimly illuminated room within the first 4 h of the dark cycle between 18:00 and 22:00 h. All the aspects of the present study were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida.

2.4. Data analysis

Defensive behaviors included freezing, kicking, startle, upright defensive posture, vocalization, escape and jump. Approach within 3 cm from the partner, sniffing of the head, body and anogenital region and other non-agonistic contacts initiated by the test mouse were categorized as social investigation. Finally, the fourth category consisted of aggressive behavior, which included bite, fight, feint, chasing the other mouse and aggressive grooming. All behaviors except social investigation were expressed as frequency per number of social interactions in order to control for variations in the number of social contacts across tests associated with drug conditions and strain differences. Social interactions were typically brief, lasting a few seconds; when the interaction persisted more than 5 s, another interaction was coded. Social investigation initiated by the subject was expressed as total frequency over the whole test (5 min). Strain differences in social-emotional behavior were analyzed by combining vehicle-treated animals used for the assessment of the effects of 7-OH-DPAT, PD 128907 and PNU 91356A. Drug effects were analyzed using two-factor analysis of variance (ANOVAs) with strain and dose as factors. Duncan's multiple range tests were performed for post-hoc analyses. A total of 40 A/J mice and 38 C57BL/6J mice were used for testing the effects of 7-OH-DPAT ($n = 6–8$ per dose), 40 A/J mice and 40 C57BL/6J mice were used for testing the effects of PD 128907 ($n = 10$ per dose) and finally, 56 A/J mice and 49 C57BL/6J mice were used for the PNU 91356A experiment ($n = 7–8$ per dose).

3. Results

3.1. Strain differences in social-emotional reactivity

Strain differences in social-emotional behavior observed for the vehicle-treated mice were similar to those reported previously [24,25]. C57BL/6J mice showed more escape (t (44) = 3.33, $P < 0.005$), upright defensive posture (t (44) = 3.35, $P < 0.005$) and aggressive behavior (t (44) = 5.25, $P < 0.001$) and less freezing (t (44) = 5.46, $P < 0.001$) and kicking (t (44) = 3.27, $P < 0.005$) than A/J mice. Finally, C57BL/6J mice investigated the partner mouse more frequently (t (44) = 4.40, $P < 0.001$) than A/J mice (data not shown). No strain differences were observed in startle, vocalization and jump under the vehicle condition.

3.2. Effects of 7-OH-DPAT on social-emotional behavior

Drug effects for each strain on a composite score of defensive behavior, aggression and social investigation are presented in Fig. 1. Table 1 depicts drug effects on individual behaviors for each strain. The ANOVA indicated a significant main effect of dose for freezing (F (5, 65) = 3.82, $P < 0.005$), startle (F (5, 65) = 2.71, $P < 0.05$) and upright defensive posture (F (5, 65) = 2.45, $P < 0.05$). A significant strain–dose interaction was found for freezing (F (5, 65) = 2.99, $P < 0.05$). This behavior increased at 0.3 mg/kg in A/J mice and at 1.0

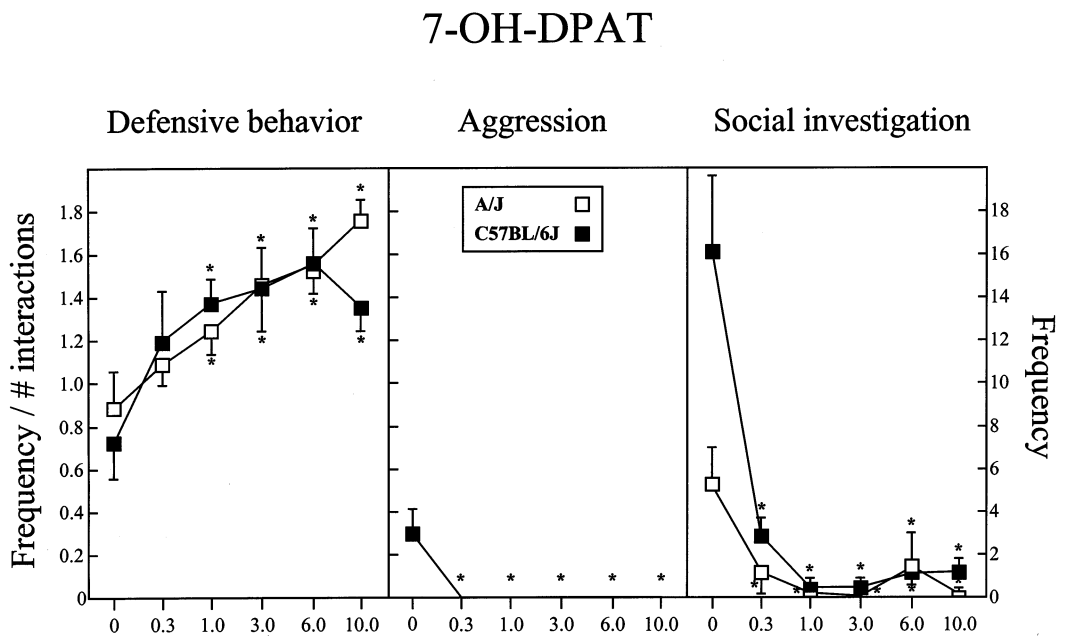

Fig. 1. Effects of 7-OH-DPAT on non-agonistic social reactivity (i.e. freezing, startle, kicking, vocalization, upright defensive posture, jump and escape; Panel A), aggressive behavior (Panel B) and social investigation (Panel C) in isolated A/J and C57BL/6J mice (mean and S.E.M.); *, $P < 0.05$; $n = 6–7$ mice per dose. Note: no aggression was observed in A/J mice.

mg/kg in C57BL/6J mice ($P < 0.05$). Although the strain by dose interaction for startle was only marginally significant (F (5, 65) = 2.08, $P = 0.08$), separate analyses conducted in each strain indicated that startle increased in A/J mice, whereas no significant increase was found in C57BL/6J mice. The increase in startle in A/J mice was significant at 6.0 and 10.0 mg/kg ($P < 0.05$). Upright defensive posture increased in both the strains at 1.0 mg/kg ($P < 0.05$).

Significant strain–dose interactions were found for escape (F (5, 65) = 5.38, $P < 0.001$) and jump (F (5, 65) = 3.35, $P < 0.01$). In C57BL/6J mice, escape was increased at 3.0, 6.0, and 10 mg/kg whereas jump was increased at 3.0 and 6.0 mg/kg ($P < 0.05$). In A/J mice, a significant increase in escape was observed at 10.0 mg/kg ($P < 0.05$).

The increase in defensive behavior following 7-OH-DPAT administration was accompanied by a decrease in aggression in C57BL/6J mice. A significant main effect of dose (F (5, 65) = 5.44, $P < 0.001$) and a significant strain by dose interaction (F (5, 65) = 5.44, $P < 0.001$) were found for this behavior. 7-OH-DPAT completely prevented the expression of aggressive behavior in C57BL/6J mice, the only strain showing aggression under the vehicle condition. The reduction was significant at all doses (Fig. 1, middle panel).

7-OH-DPAT also decreased social investigation in A/J and C57BL/6J mice (F (5, 65) = 23.51, $P < 0.001$). As seen in Fig. 1 (right panel), this effect was greater in C57BL/6J mice, given the higher level of social investigation observed in this strain under the vehicle condition. This was revealed by a significant strain–dose

Table 1
Effects of 7-OH-DPAT, PD 128907 and PNU 91356A on social-emotional behaviors in A/J and C57BL/6J mice

Behavior	A/J			C57BL/6J		
	7-OH-DPAT	PD 128907	PNU91356A	7-OH-DPAT	PD 128907	PNU91356A
Freezing	↑ (0.3)	–	–	↑ (1)	–	–
Upright	↑ (1)	–	–	↑ (1)	–	–
Kicking	–	–	↑ (10)	–	–	↑ (0.1)
Startle	↑ (6, 10)	–	–	–	–	–
Vocalization	–	–	–	–	–	–
Jump	–	–	–	↑ (3, 6)	↑ (3)	↑ (10)
Escape	↑ (10)	↑ (3)	–	↑ (3, 6, 10)	↑ (1,3)	
Attack	–	–	–	↓ (0.3–10)	↓ (0.3–3)	↓ (0.1–10)
Investigation	↓ (3, 6, 10)	↓ (0.3–10)	↓ (0.03–10)	↓ (0.3–10)	↓ (0.3–3)	↓ (0.3–10)

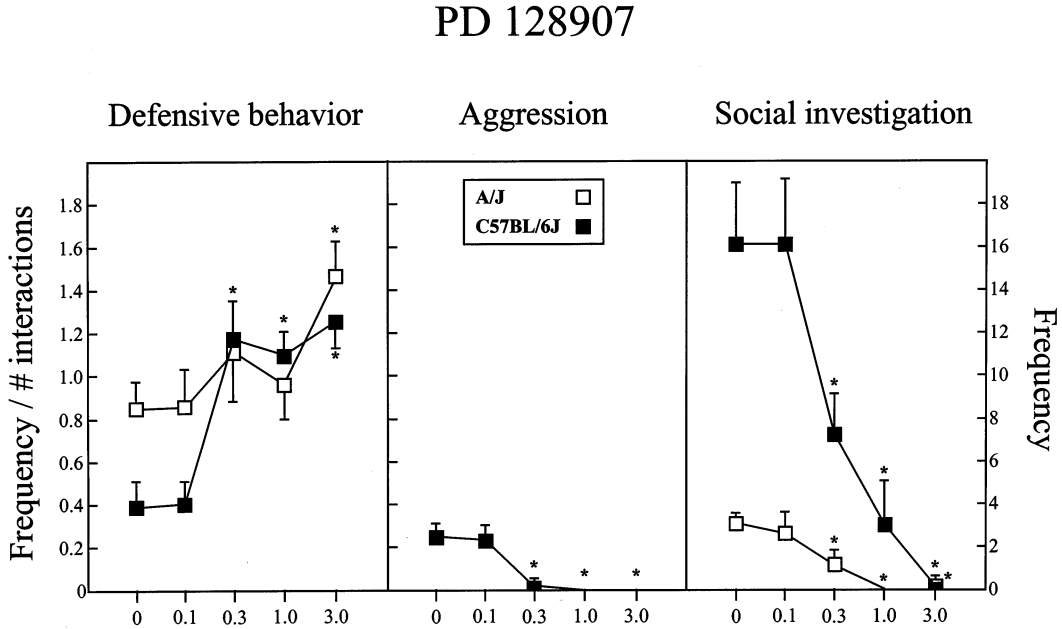

Fig. 2. Effects of PD 128907 on non-agonistic social reactivity (i.e. freezing, startle, kicking, vocalization, upright defensive posture, jump and escape; Panel A), aggressive behavior (Panel B) and social investigation (Panel C) in isolated A/J and C57BL/6J mice (mean and S.E.M.); *, $P < 0.05$; $n = 10$ mice per dose. Note: no aggression was observed in A/J mice.

interaction (F (5, 65) = 6.55, $P < 0.001$). In C57BL/6J mice, these reductions were significant at all doses, whereas social investigation was decreased in A/J mice at 3.0, 6.0 and 10.0 mg/kg ($P < 0.05$).

3.3. Effects of PD 128907 on social-emotional behavior

As indicated in Fig. 2 (left panel), PD 128907 significantly increased defensive behavior in both strains. The ANOVA revealed significant drug effects for jump (F (4, 70) = 7.33, $P < 0.001$) and escape (F (4, 70) = 9.26, $P < 0.001$). Jump was increased at 3.0 mg/kg ($P < 0.05$) but only in C57BL/6J mice as a significant strain–dose interaction was found for this behavior (F (4, 70) = 5.00, $P < 0.001$). Similarly, a marginal strain–dose interaction was found for escape (F (4, 70) = 2.28, $P = 0.07$). Escape was increased at 3.0 mg/kg in A/J mice and at 1.0 and 3.0 mg/kg in C57BL/6J mice. The ANOVA also indicated a significant drug effect for upright defensive posture (F (4, 70) = 2.77, $P < 0.05$) but post-hoc comparison failed to show any significant differences between the doses.

PD 128907 decreased the aggressive behavior (F (4, 35) = 8.07, $P < 0.001$) and social investigation (F (4, 35) = 9.39, $P < 0.001$) in C57BL/6J mice. As seen in Fig. 2 (middle and right panels), these behaviors were reduced at 0.3, 1.0 and 3.0 mg/kg ($P < 0.05$).

3.4. Effects of PNU 91356A on social-emotional behavior

As seen in Fig. 3 left panel, the D_2 agonist did not affect defensive behavior in C57BL/6J mice whereas in A/J mice a significant increase was observed only at 3.0 mg/kg. Analysis of each behavioral item indicated a significant main effect of dose on freezing (F (6, 91) = 2.82, $P < 0.05$) and marginally significant dose effects on startle (F (6, 91) = 2.05, $P = 0.07$) and kicking (F (6, 91) = 2.11, $P = 0.06$). The effects of PNU 91356A on freezing were strain specific as a significant strain–dose interaction was observed (F (6, 91) = 2.30, $P < 0.05$). However, none of these effects reach statistical significance ($P > 0.05$). Similarly, a significant strain–dose interaction was found for startle (F (6, 91) = 3.51, $P < 0.005$) but again post-hoc comparisons failed to reach significance. Finally, the ANOVA yielded a significant strain–dose interaction for kicking (F (6, 91) = 3.01, $P < 0.01$), which increased at 10.0 mg/kg in A/J mice and at 0.1 mg/kg in C57BL/6J mice ($P < 0.05$).

Significant dose effects were found for jump (F (6, 91) = 2.75, $P < 0.05$) and escape (F (6, 91) = 2.84, $P < 0.05$). Jump increased in C57BL/6J mice at 10 mg/kg whereas no significant effect was observed in A/J mice. This strain difference was reflected by a significant strain–dose interaction (F (6, 91) = 2.78, $P < 0.05$). On the other hand, post-hoc comparisons did not indicate any significant differences in escape behavior in either strain.

PNU 91356A decreased aggressive behavior (F (6, 91) = 2.61, $P < 0.05$) and social investigation (F (6, 91) = 16.90, $P < 0.001$). Significant strain–dose interactions were found for both aggressive behavior (F (6, 91) = 2.61, $P < 0.05$) and social investigation (F (6,

91) = 16.90, $P < 0.001$). As seen in Fig. 3 (middle and right panels), both aggressive behavior and social investigation were reduced from 0.1 to 10.0 mg/kg ($P < 0.05$) in C57BL/6J mice. Consistent with the earlier results, no aggression was observed in A/J mice under vehicle or drug conditions. Social investigation was reduced in all the doses in this strain ($P < 0.05$).

4. Discussion

This study examined the effects of D_3 and D_2 DA receptor agonists on social-emotional behavior in isolated C57BL/6J and A/J mice. Two related hypotheses were tested. First, since D_3 DA receptors are particularly enriched in mesolimbic areas and have been suggested to be involved in emotional function [9,66,73], it was hypothesized that the D_3 receptor agonists 7-OH-DPAT and PD 128907 would alter (decrease and/or increase) social-emotional reactivity more specifically than the selective D_2 receptor agonist PNU91356A. A second hypothesis was that the effects of the DA agonists on social-emotional reactivity would be greater in A/J mice than in C57BL/6J mice. This hypothesis was based on a previous study, showing that the D_2/D_3 DA agonist quinpirole markedly increased the defensive behavior in A/J mice and had only marginal effects in C57BL/6J [25].

As hypothesized, the D_3 receptor agonists 7-OH-DPAT and PD 128907 were highly effective in altering defensive behavior. To our surprise, however, these effects were apparent particularly in C57BL/6J mice. Indeed, the most prominent effect of the D_3 receptor agonists in this strain was a marked increase in escape and jump at higher doses, an effect very similar to what has been observed after administration of D_1-like agonists in this strain [24]. In A/J mice, escape behavior was also increased by the D_3 receptor agonists, but these effects were far less pronounced than in C57BL/6J mice. Escape behavior was not significantly increased in either strain after administration of the selective D_2 receptor agonist PNU91356A or with quinpirole as previously observed [25]. In fact, the behavioral effects of PNU91356A were highly similar to those obtained with quinpirole. These results indicate that quinpirole may exhibit greater in vivo affinity for D_2 receptors than for D_3 receptors.

In tests of locomotor activity, systemic administration of D_3 receptor agonists has been shown to depress locomotion over a wide dose range [1,13,37,59,74,77]. In some studies, locomotor activity returned to baseline levels or higher as the doses increased, an effect hypothesized to reflect activation of post-synaptic D_2 receptors [13,59,74]. If activation of post-synaptic D_2 receptors stimulates locomotor behavior, one would expect PNU 91356A and quinpirole to facilitate the expression of escape behavior. However, this was not the case.

If activation of D_2 receptors was not sufficient to induce escape behavior, one may ask what caused the stimulatory effects of higher doses of 7-OH-DPAT and PD 128907 on this behavior. The stimulatory effects of

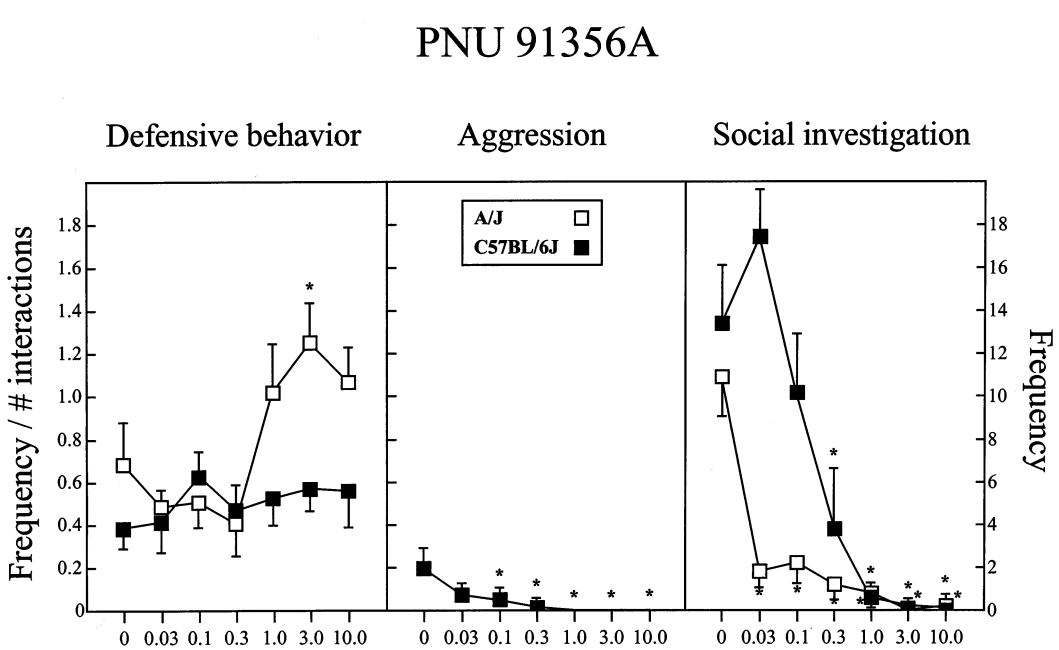

Fig. 3. Effects of PNU 91356A on non-agonistic social reactivity (i.e. freezing, startle, kicking, vocalization, upright defensive posture, jump and escape; Panel A), aggressive behavior (Panel B) and social investigation (Panel C) in isolated A/J and C57BL/6J mice (mean and S.E.M.); *, $P < 0.05$; $n = 7–8$ mice per dose. Note: no aggression was observed in A/J mice.

7-OH-DPAT and PD 128907 are unlikely to be mediated by D_1 or D_4 DA receptors since these agonists display very low affinity for these receptor subtypes [42,59]. In addition, although 7-OH-DPAT binds with high affinity to sigma receptors [65], PD 128907 has very low affinity for these receptors as well as for serotonergic and adrenergic receptors [59]. Accordingly, the stimulatory effects of higher doses of the D_3 agonists on escape behavior probably did not involve D_1 and D_4 DA receptors or the serotonergic and adrenergic systems.

Although PNU 91356A showed a 50-fold selectivity for D_2 over D_3 receptors [57] and quinpirole's selectivity for D_3 over D_2 receptors has been generally reported to be lower than those of PD 128907 and 7-OH-DPAT [4,31,45,59,68,77], doubts have been raised concerning the affinity of these D_3 receptor ligands for this receptor subtype under in vivo conditions [28,40,44]. In addition, not only are D_3 receptors expressed at much lower levels than D_2 receptors [41,55,66], but also given the higher affinity for D_3 than for D_2 receptors by DA [73], D_3 receptors are preferentially occupied by the endogenous transmitter, thereby, reducing the number of D_3 sites available for the agonist [44,83]. Nevertheless, the behavioral effects observed at higher doses of the putative D_3 receptor agonists 7-OH-DPAT and PD 128907 in the social interaction test differed from those of the selective D_2 receptor agonist PNU 91356A and quinpirole. As mesolimbic areas have a greater D_3/D_2 receptor ratio than striatal regions [9,54,66,73], it is possible that the efficiency of 7-OH-DPAT and PD 128907 at potentiating escape behavior reflects their higher affinities for limbic D_2-like (possibly D_3) DA receptors [44].

These results suggest that D_3 DA receptors play a stimulatory role on emotional behavior. This hypothesis is supported by the finding that D_3 DA receptor knockout mice showed less 'anxiety-like' activity in the open field and elevated plus-maze [75]. Recent studies, however, have shown that putative D_3 receptor agonists and antagonists have similar effects on locomotor activity and body temperature in D_3 DA receptor knockout mice and wild-type mice [8,86]. These findings indicated that D_3 receptors may not be involved in the behavioral effects induced by putative D_3 receptor ligands. For this conclusion to be generalized to the expression of emotional behavior, however, it would be necessary to test the pharmacological effects of putative D_3 receptor ligands in D_3 receptor mutant and wild-type mice in settings where various emotional behaviors can be induced. In the present study, we observed that all DA agonists have similar hypolocomotor effects prior to social exposure. Although, we did not quantify these observations, differences between agonists were apparent only in response to social-emotional stimuli.

The present data contrast with previous results, indicating no specific effects on emotional behavior in the elevated plus-maze for both D_3 and D_2 receptor agonists [62,63]. Several factors may explain this discrepancy. First, strain is an important variable in the effects of DA agonists on motor and emotional behavior [17,24,25,67,70], also see [48] for the differential effects of benzodiazepine ligands in C57BL/6J and A/J mice. As mentioned above, the nature of the test situation is another key factor. In this regard, it may be judicious to investigate the effects of dopaminergic ligands on emotional behavior in test situations that allow the discrimination of the effects on motor function from the effects on emotional behavior. For instance, Franklin and Tang [18] reported important motor depressant effects in rats in the *Y*-maze following administration of D_2/D_3 receptor agonists, but when mild electrical shocks were applied through the grid floor, locomotor suppression was replaced by intense locomotor reactivity. These results indicate that the effects of DA agonist on emotional behavior are mediated by mechanisms at least partially different from those associated with motor function [52,53].

Nevertheless, the expression of emotional behavior is significantly dependent on motor function and strain differences or alteration in motor function by DA agonists are likely to modulate the expression of social-emotional behavior. C57BL/6J mice and A/J mice have been characterized by high and low levels of motor activity, respectively [48,71,80]. It is, therefore, not surprising that following social isolation C57BL/6J mice primarily exhibited locomotor forms of defensive behavior (e.g. escape) whereas A/J mice showed more stationary reactivity (e.g. freezing). Given their higher levels of locomotor reactivity, C57BL/6J were thus, greatly affected by the hypolocomotor effects of the DA agonists. This was particularly evident at lower doses of the D_2-like DA receptor agonists. Indeed in this strain, escape tended to be reduced at lower doses, whereas stationary forms of defensive behavior, that is, reactivity not requiring displacement of the animal (e.g. freezing, upright defensive posture, kicking) were increased. This is a good illustration of how alterations in motor function may influence the expression of emotional behavior. Conversely, in A/J mice, which exhibited very low levels of locomotor activity under vehicle conditions, the depressant (and stimulant) effects of DA agonists on motor function only minimally affected the expression of social-emotional reactivity. Accordingly, the use of two strains that differ in motor activity may help in differentiating the effects of drugs on motor function from the effects on emotional function.

A previous report indicated that D_3 agonists reduced ultrasonic vocalization in rats at lower doses [5]. These results suggested the possibility that activation of D_3 autoreceptors may reduce anxiety in this paradigm and in this species. No anxiolytic-like effects were observed

at lower doses in the present study. Instead, the DA agonists increased the social-emotional reactivity over a wide dose range, even at lower doses. On the other hand, all DA agonists considerably reduced the frequency of social investigation initiated by the test mouse. This was seen in both strains and over a wide dose range. However, this was not the only consequence of the effects on motor function as social investigation was reduced at doses that also increased escape behavior. Similar effects on aggression were observed in C57BL/6J mice, the only one of the two strains exhibiting aggressive behavior under vehicle conditions. These reductions in social investigation and aggressive behavior and the parallel increase in defensive behavior suggest that activation of DA receptors increased fearfulness. In this paradigm, however, reactivity was elicited by mild social stimulation initiated by the conspecific rather than clearly threatening or painful stimuli. Therefore, this may be even more related to anxiety or other states involving dysregulated social behavior (e.g. social phobia).

The effects of D_2-like dopamine antagonists on social behavior have been also investigated. In C57BL/6J mice that had been repeatedly defeated and then exposed to a non-aggressive unfamiliar mouse, the D_2-like antagonist sulpiride reduced escape behavior and upright defensive behavior while increasing crouch (i.e. freezing) and social investigation [58]. Another experiment in OF-1 mice indicated that sulpiride reduced isolation-induced aggression [60]. Similar anti-aggressive effects were found in isolated OF-1 mice with the D_2-like antagonists raclopride [2] and in isolated Swiss mice with eticlopride [16]. On the other hand, a study in isolated OF-1 mice [15] indicated that the D_4 receptor antagonist clozapine increased aggression and decreased defensive behavior (e.g. freezing and kicking). In addition, social investigation was augmented and defensive behavior reduced in intruder OF-1 mice facing an aggressive resident conspecific. Finally, in a previous study, we observed that the putative D_3 receptor agonist PNU 99194A reduced aggression in isolated C57BL/6J mice [26]. The decrease in aggression, however, was associated with a substantial increase in defensiveness as represented by higher frequencies of escape behavior, startle and vocalization. Although these studies seems to indicate specific roles for the different DA receptor subtypes in mediating social-emotional behavior, it would be hazardous to make any conclusion based on the effects of a few putative ligands that may exhibit poor in vivo selectivity.

It is important to recall that the present experiments were conducted on individually caged mice. Previous reports indicated that social isolation upregulated both D_1-like [21,22] and D_2-like [32] DA receptor subtypes. Isolated animals have been shown to be more sensitive to the motor effects of DA agonists [3,42,64,84,85]. Similarly, the effects of DA agonists on social-emotional reactivity were found to be absent or less pronounced in group-housed mice [22,25,58]. These results are consistent with the hypothesis that DA potentiates the organism's motor-emotional response to novel stimuli [6]. The present results also suggest that alterations in DA receptor function may be, at least in part, responsible for the modified emotional threshold characteristic of isolated animals. No data are currently available on the effects of social isolation on D_3 DA receptors and further studies are necessary to examine this issue. For instance, it would be interesting to investigate and compare the effects of isolation housing in D_3 receptor knockout mice versus wild-type mice. Based on previous [75] and present results, D_3 receptor knockout mice would be expected to exhibit lower levels of social-emotional reactivity after isolation. In addition, selective D_3 DA agonists would be expected to be less effective in increasing social-emotional reactivity in D_3 receptor knockout mice. DA receptor mutant mice are often produced using a C57BL/6J mouse line. The present findings are, therefore, a pertinent first step in the identification of relationships between DA receptor subtypes and specific social-emotional behavior. Despite the limits of the current pharmacological tools and the pitfalls of gene targeting methods [27], these proposed studies would probably contribute to the understanding of the putative role of D_3 receptors in the mediation of emotional behavior.

Acknowledgements

This research was supported in part by a Natural Science and Engineering Research Council of Canada Scholarship to PLG and a PHS Grant (NS-34363) to JMP. We wish to thank Pharmacia and Upjohn for their generous gifts of PNU 91356A.

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