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Rearing Conditions Alter Social Reactivity and D_1 Dopamine Receptors in High- and Low-Aggressive Mice

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GARIÉPY, J.-L., P. L. GENDREAU, R. B. MAILMAN, M. TANCER AND M. H. LEWIS. *Rearing conditions alter social reactivity and D_1 dopamine receptors in high- and low-aggressive mice.* PHARMACOL BIOCHEM BEHAV **51**(4) 767-773, 1995.—As a result of selective breeding, NC900 mice exhibit isolation-induced attacks in a social interaction test, whereas NC100 mice do not attack but freeze instead. Administration of the D_1 receptor agonist dihydrexidine was previously shown to reduce aggression in NC900 mice and nonagonistic approaches in NC100 mice. This resulted from induction of a marked social reactivity in both selected lines. Because isolation rearing also induces social reactivity, the present experiment was designed to test the hypothesis that D_1 dopamine receptors mediate isolation-induced social reactivity. Isolation was expected to potentiate the effects of a D_1 agonist and to increase D_1 dopamine receptor density. Thus, isolated and group-reared mice were administered dihydrexidine, and their social behavior was compared to vehicle-injected controls. Dihydrexidine induced higher levels of reactivity among isolated than among group-reared animals, especially in NC900 mice. In independent experiments, increased densities of D_1 dopamine receptors in the striatum of isolated animals were found, with no change in affinity. These studies suggest an important role for the D_1 dopamine receptor as a mediator of isolation-induced social reactivity.

Reactivity Aggressive behavior Rearing conditions D_1 dopamine receptor Striatum Dihydrexidine

THE LITERATURE on behavior genetics demonstrates that numerous behavioral characteristics, including open field activity, alcohol consumption, "emotionality," and aggression are readily amenable to genetic selection (5). The establishment of lines of animals that differ on selected characteristics constitutes a useful technique for examining how the central nervous system mediates the interaction of experience with genetic background in the expression of individual differences. We have been involved in a selective breeding experiment that is now in its 26th generation. This research program was initiated more than 2 decades ago by Cairns and his collaborators, who have selectively bred Institute for Cancer Research (ICR) mice for high and low levels of aggression (3).

Selection effects appeared rapidly, with robust line differences in attack obtained by the fourth (S_4) generation [see also (10,17) for similar results]. Although the selective breeding program was aimed at developing lines with both high- and low-aggressive characteristics, relatively little change has been observed in the high-aggressive line (NC900). Across the successive generations of selective breeding, the level of aggression in this line never departed significantly from the level observed in the foundational (S_0) generation or in isolated, randomly bred ICR mice. Line differentiation occurred principally as a result of the rapid decrease of attacks in the low-aggressive line (NC100) and the stabilization of frequencies near zero in subsequent generations (3,7). Those mice selected for low aggression now rarely exhibit the aggression expected of this mouse strain following individual housing. Instead of

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attacking, NC100 mice exhibit a strong tendency to freeze and to become immobile (i.e., social inhibition) when exposed to an unfamiliar group-housed male of the same ICR strain.

Although the line differences are robust and have been replicated in every generation since S_4, a most effective manipulation whereby the differences in aggressive behavior can be altered is through a simple change in rearing condition. The effects of selective breeding are not easily observable when, following weaning, the animals are reared with other males instead of being singly caged. Under such rearing conditions, high-aggressive animals rarely attack an unfamiliar mouse, and no line differences are observed in social interactions. Analyses of the behavioral differences observed at puberty (45 days of age) between mice that have been reared under each condition showed that isolated males tend to react much more strongly to novel stimuli than males reared in groups. Specifically, isolated subjects of both lines are easily startled by tactile stimulation, whereas group-reared subjects seem to simply ignore the same stimulation. A similar effect is observed in response to social stimulation where the isolated males exhibit strong reactive responses to the mild investigatory approaches of the other mouse (2). In addition, the tendency to freeze in response to social stimulation, normally observed among isolated NC100 mice, is virtually absent among males that have been reared in groups.

Previous studies of central dopaminergic function indicated that line differences in dopamine concentrations and dopamine receptor densities may mediate some of the behavioral differences observed between the high- and the low-aggressive lines. This research showed that compared to the high-aggressive line, low-aggressive mice have lower dopamine concentrations in nucleus accumbens and caudate nucleus (12), with increased dopamine receptor densities in these same regions (4). To determine which behavioral system, social inhibition (freezing) or social reactivity, may be affected by these neurochemical differences, we examined how the social behavior of each line may be differentially affected by administration of the full efficacy D_1 dopamine agonist, dihydrexidine. This manipulation showed that dihydrexidine dose-dependently reduced attacks in the high-aggressive line and similarly reduced nonagonistic approaches in the low-aggressive line. In both cases, the effects were related to a marked increase in reactivity to the mild social stimulation provided by the partner mouse, as measured by increases in behaviors such as escape, reflexive kicking, and vocalization. In independent experiments, it was shown that selective blockade of D_1, but not D_2, dopamine receptors, prior to the administration of dihydrexidine, significantly antagonized the effect of the drug. Consistent with previous findings on behavioral line differences (6,8), dihydrexidine appeared to induce higher levels of reactivity in the high-aggressive line. Taken together, the results suggested an important role for the D_1 dopamine receptor in the emotional response to social or other environmental stimulation (11).

Because a major outcome of isolation rearing is to augment social reactivity to novel stimulation beyond the level observed among group-housed animals, the above findings suggested that dihydrexidine treatment would have less effect on the social behavior of mice reared in groups, but would induce high levels of reactivity among isolated mice. Because of the known line differences in isolation-induced reactivity, the response to a dihydrexidine challenge was expected to be more strongly affected by rearing conditions in the high-aggressive line than in the low-aggressive line. A corollary of these hypotheses was that mice reared in isolation would show increased densities of D_1 dopamine receptors relative to group-housed mice, and that the isolation-induced increase would be greater in NC900 than in NC100.

METHOD

Selection and Rearing

In the foundational generation of the selective breeding research, ICR male mice that attacked most rapidly and frequently in a social interaction test were identified, and they were subsequently mated with females that were nonlittermates but whose brothers had also been selected for high levels of attack. From the first selection generation onward, the males that failed to attack were, in each generation, removed from the reproduction colony for that line (NC900), along with the females of the same litters. Exactly comparable procedures were followed in establishing the low-aggressive line (NC100), except that low-aggressive males were selected and more aggressive ones were eliminated. Thus, attack behavior among the males was the only criterion for selection. Earlier reports have detailed the breeding criteria, and the outcomes over early and late generations (3,7). In each generation, male mice, after weaning at 21 days of age, were either reared in individual cages or reared in clear opaque cages with three same-line males until they were observed interacting with an unfamiliar mouse at 45 days. During this period, isolated animals had no social contact other than exposure to the noises and odors produced in the colony room. Conversely, animals that served as test partners were placed in clear plastic cages containing four unrelated males. These animals were derived from the same ICR foundational stock, except that they were propagated without selection throughout the research program. Details of these methods and housing procedures have been described previously (3,7).

The animals used in the present experiment were born in the 26th generation (S_{26}) of the selective breeding program. All mice had access to food ad lib and were kept on a reverse light cycle (12L : 12D) with the dark onset beginning at 0900 h. Male and female littermates were kept together with their mother until 21 days of age, when they were sex typed, weaned, and assigned to the appropriate experimental rearing condition (see below).

Social Interaction Test

In the social interaction test, each subject was placed alone for 5 min in one side of a Plexiglas compartment (20 × 21 × 31 cm) to habituate to the test environment. A sliding sheet-panel wall was then removed, exposing the subject to a same-age, group-reared male (marked for identification) that had been placed in the other half of the compartment. In the succeeding 10 min, all social interactions were recorded after which both animals were weighed and returned to their home cages. This behavioral testing was conducted between 1400 and 1600 h in a dimly illuminated room.

The behaviors of both the test and the partner mouse were scored. This continuous scoring technique allowed us to code: (a) the behavior of the test animal toward its partner, including initiation of behaviors and the responses to those behaviors, and (b) the sequence in which the social events occurred, including interactions between animals, and autocorrelated states within animal (7). The behavioral categories of interest to the present study are described in Table 1. For the several generations in which these categories have been used, interobservers agreement has always exceeded 90%. All behavioral

TABLE 1

BEHAVIORAL CATEGORIES CODED IN THE SOCIAL INTERACTION TEST

Behavioral Category	Definition
Attack	Vigorous lunge toward the other animal, with biting or slashing
Freeze	Immobile and seemingly frozen, upon and following social stimulation
Nonagonistic	Sniffing the other animal, climbing on its head or back
Startle	Reflexive jerk backward of the head and front paws
Kick	Reflexive, rapid extension of the rear paw when approached or touched
Vocalize	High-pitched, species-typical sound when approached or touched
Escape	Rapid retreat, running away
Jump	Rapid upward movement with all four paws leaving the ground

procedures were conducted by observers who were uninformed as to which selected lines were represented in the test.

Dihydrexidine-Induced Behavior: Rearing Effects

The effects of rearing condition upon dihydrexidine-induced behaviors were examined by contrasting for each selected line the dyadic interactions of mice that had been singly caged or reared in groups. In the isolation rearing condition, 12 subjects from each line served as vehicle-injected controls (VEH) and 12 were injected (SC) with 10 mg/kg of dihydrexidine (DHX). This dose was determined on the basis of a previous study where it had been shown to induce high levels of social reactivity without altering activity rates or inducing stereotypies (11). Under the group-rearing condition, eight subjects from each line served as controls. For this condition, 8 low-aggressive and 10 high-aggressive animals were administered dihydrexidine. The social interactions of these animals in a dyadic test were scored as described above.

Attack, freezing, and nonagonistic initiations were expressed as the number of 5-s blocks in which the behavior occurred over the 10-min test period. Behaviors indicative of reactivity (e.g., startle, vocalization, reflexive kicking, jump, and escape) were scored as rates per minute. The frequency of these behaviors was calculated over the first 2 min of interactions or before the initiation of an agonistic action (e.g., feint, bite, attack) by one of the animals. This procedure was adopted because previous studies have shown that the test animals tend to become more reactive following attacks and defeats (2). Thus, rates per minute of preagonistic activity were calculated to permit comparisons across test sessions and to disentangle rearing and drug effects from agonistic effects. The observers were uninformed of both drug and rearing condition represented in the test. Data (frequency and rates per minute) were subjected to three-factor (2 × 2 × 2) analyses of variance to test for line, rearing conditions, drug, and their interactions.

D_1 Dopamine Receptor Binding

Forty animals per line were placed either in individual cages or in groups at weaning and sacrificed by decapitation at day 45 without being exposed to a social interaction test. Their brains were rapidly removed, frozen on powdered dry ice with care taken to avoid compression of the dorsal or ventral surface, and stored at −80°C until assayed. Estimates of the relative affinity (K_d) and density (B_{max}) of D_1 dopamine receptors sites in the corpus striatum (caudate nucleus and putamen) were determined using Scatchard analyses of saturation isotherms generated from radioligand binding studies. Using four to five nonlittermates from each line per assay, six Scatchard plots were generated for each housing condition for each line.

Dissected striata were pooled and homogenized in 10 ml of ice-cold 50 mM HEPES buffer, pH 7.4 (4°C), using Teflon-glass homogenizers. Tissue was centrifuged at 27,000 × *g* for 10 min, the supernatant was discarded, and the pellet was resuspended in 10 ml ice-cold buffer and centrifuged again. The final pellet was suspended at a concentration of approximately 10.0 mg wet weight/ml. Assay tubes (1 ml final volume) were incubated at 37°C for 20 min. Nonspecific binding of [^{3}H]SCH23390 was defined by adding unlabeled SCH23390 at a concentration of 10 μM. Binding was terminated by filtering with 15 ml ice-cold buffer on a Skatron cell harvester (Skatron Inc., Sterling, VA) using glass fiber mats (Skatron #7034, Sterling, VA). Filters were allowed to dry, and 3.0 ml of Scintiverse E (Fisher Scienctifc Co., Fair Lawn, NJ) was added. After shaking for 30 min, radioactivity was determined on a LKB RackBeta liquid scintillation counter. Six concentrations ranging from 0.025 to 2.5 nM [^{3}H]SCH23390 were used for the saturation isotherms. Tissue protein levels were estimated using a colorimetric assay.

RESULTS

Effects of Rearing Conditions on Dihydrexidine-Induced Behaviors

The frequencies of social behaviors observed for the vehicle-injected animals reared in groups or in social isolation were essentially the same as those obtained in previous generations of selective breeding [see (2,7)]. Attack frequencies (Fig. 1) were significantly lower in the dyadic tests involving low-aggressive subjects, $F(1, 107) = 22.6$, $p < 0.001$, and were significantly reduced among animals of both lines that were

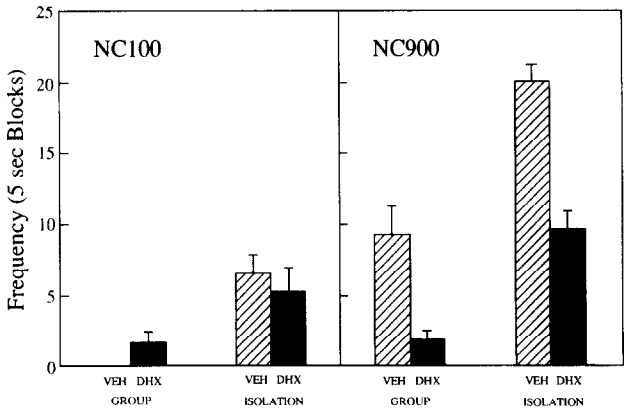

FIG. 1. Effects of rearing conditions (group, isolation) on dihydrexidine (DHX; 10 mg/kg)-induced behavior. Mean frequency (number of 5-s intervals) of attacks (± SEM) in mice selectively bred for high (NC900) and low (NC100) levels of aggression.

reared in social groups, $F(1, 107) = 13.4$, $p < 0.001$. As expected, dihydrexidine reduced attacks in both lines, $F(1, 107) = 7.3$, $p < 0.01$, and did so to a greater extent in NC900 mice, as indicated by the statistically significant line by drug interaction, $F(1, 107) = 6.3$, $p < 0.05$. The drug had a similar effect on individually or group-reared animals, and no significant interaction was found between these two factors.

Figure 2 shows that the characteristic difference between the high- and the low-aggressive lines in the propensity to freeze upon social contact was clearly expressed among animals born in the 26th generation, $F(1, 107) = 16.4$, $p < 0.001$. The effects of rearing conditions on freezing also replicated previous studies (2) in that, by contrast to animals reared in isolation, virtually no freezing was observed among group-reared animals of either line, $F(1, 107) = 10.6$, $p < 0.01$. The strong effects of rearing condition on this behavior in NC100 mice yielded a significant line by rearing interaction, $F(1, 107) = 6.5$, $p < 0.05$. Although the occurrence of freezing was somewhat reduced among drug-treated animals, no significant effect of dihydrexidine was found and none of the interactions involving the variable drug reached significance. In a previous study, dihydrexidine had been similarly shown to have no detectable effect on this behavior (11).

As expected from studies of nontreated animals of previous generations, both isolated and group-reared NC100 mice exhibited significantly higher frequencies of nonagonistic approaches toward the partner mouse than did NC900 mice, $F(1, 107) = 38.9$, $p < 0.001$. These behaviors constituted mild social stimulations and typically involved sniffing the partner mouse or climbing on its head or back. Rearing conditions differentially affected the frequency of these approaches in the two lines, $F(1, 107) = 8.4$, $p < 0.01$. Although for NC900 mice such approaches were most frequent in the tests involving group-reared animals, the highest frequencies in NC100 mice were observed for the isolated subjects. Dihydrexidine more than halved the number of nonagonistic approaches, $F(1, 107) = 28.4$, $p < 0.001$. As seen in Fig. 3, this effect was consistent across all subjects, irrespective of selected line or rearing condition, such that no significant interaction involving drug treatment was found.

It was hypothesized that the major effects of rearing condition on dihydrexidine-induced behaviors would be found for

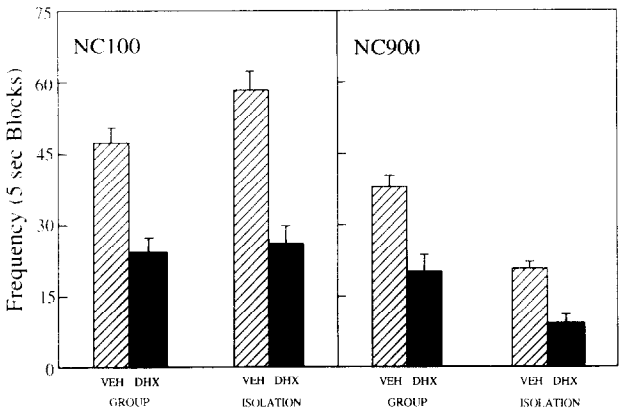

FIG. 3. Effects of rearing conditions (group, isolation) on dihydrexidine (DHX; 10 mg/kg)-induced behavior. Mean frequency (number of 5-s intervals) of nonagonistic approaches (±SEM) in mice selectively bred for high (NC900) and low (NC100) levels of aggression.

indices of social reactivity, namely, those within-animal, autocorrelated states that are expressed as a propensity to react strongly to the mild social stimulation provided by the partner mouse. These indexes, described in Table 1, include the actions of escaping, jumping, kicking, vocalizing, or being startled in response to mild social stimulation. It was established in previous research that NC900 mice are somewhat more reactive than NC100 animals, although some forms of reactivity tend to be line specific [e.g., reflexive kicking in NC100 mice and jumping and escaping in NC900 mice (6)]. In the present study, the rates of startle-withdrawal and jump were quite low across all conditions and, hence, not subjected to individual analysis.

As expected on the basis of Lewis et al. (11), the decrease in attack behavior and nonagonistic approaches observed among dihydrexidine-treated animals was related to an increase in social reactivity. This effect is seen in Fig. 4, which shows that reflexive kicking was observed significantly more often among dihydrexidine-treated animals than among nontreated ones, $F(1, 107) = 13.4$, $p < 0.001$. The line difference for this in-

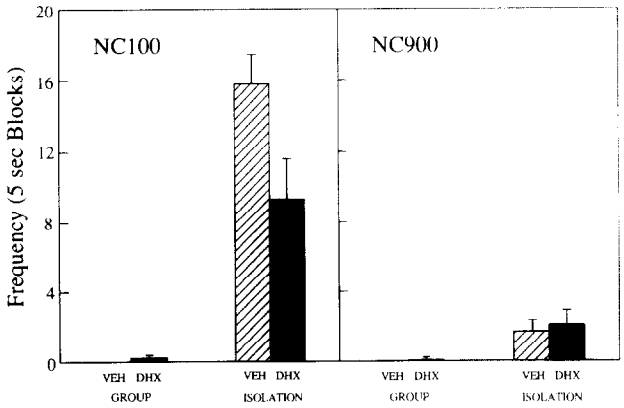

FIG. 2. Effects of rearing conditions (group, isolation) on dihydrexidine (DHX; 10 mg/kg)-induced behavior. Mean frequency (number of 5-s intervals) of freezing (±SEM) in mice selectively bred for high (NC900) and low (NC100) levels of aggression.

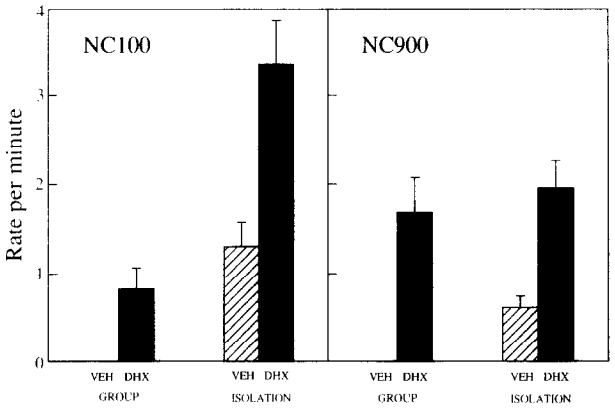

FIG. 4. Effects of rearing conditions (group, isolation) on dihydrexidine (DHX; 10 mg/kg)-induced increases in kicking in mice selectively bred for high (NC900) and low (NC100) levels of aggression. Data are expressed as rate per minute (mean ± SEM).

dex of reactivity did not reach significance, although the higher rates observed in isolated NC100 mice were in the expected direction. In both lines, animals reared in groups exhibited significantly less kicking than those reared in isolation, $F(1, 107) = 5.9$, $p < 0.05$. The effects of dihydrexidine on this behavior tended to be more pronounced among isolated than group-reared animals, but the hypothesized rearing by drug interaction was not found.

Figure 5 confirms the tendency toward a line difference in reactivity and shows that NC900 mice exhibit a stronger tendency to vocalize upon mild social contact than the NC100 line, $F(1, 107) = 5.8$, $p < 0.05$. This difference, however, was evident only among isolated animals administered drug, as indicated by the significant line by rearing by drug interaction, $F(1, 107) = 5.1$, $p < 0.05$. In fact, very little difference was observed among dihydrexidine-treated NC100 mice that were reared in group or in isolation. The separate analyses conducted independently for each line confirmed that the modulating effect of rearing condition on dihydrexidine-induced vocalization holds for the high-aggressive line only [NC100: $F(1, 51) = 0.1$, $p > 0.05$; NC900: $F(1, 55) = 6.2$, $p < 0.05$].

As seen in Fig. 6, there was a tendency among isolated NC900 mice to escape more frequently from the nonagonistic approaches of the partner mouse, although the line difference was not significant ($p > 0.05$, two-tailed). To the extent that it was never observed among group-reared animals of either line, this form of social reactivity was strongly affected by rearing conditions, $F(1, 107) = 10.6$, $p < 0.01$. Moreover, in both lines dihydrexidine induced higher rates of escape, $F(1, 107) = 10.6$, $p < 0.01$. The magnitude of this effect was strongly contingent upon the rearing histories of the subjects, so that the drug had no detectable effect upon group-reared animals. Only those subjects reared in isolation showed the expected drug-induced increase in escape, $F(1, 107) = 6.3$, $p < 0.05$. Although the three-way interaction was not significant, separate analyses conducted independently for each line showed that the evidence for a modulating effect of rearing condition on drug-induced escape was entirely due to the significant rearing by drug interaction in the high-aggressive line [NC100: $F(1, 51) = 1.97$, $p > 0.05$.; NC900: $F(1, 55) = 4.3$, $p < 0.05$].

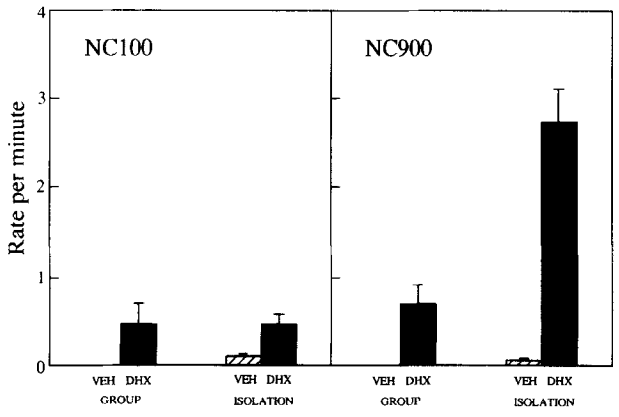

FIG. 5. Effects of rearing conditions (group, isolation) on dihydrexidine (DHX; 10 mg/kg)-induced increases in vocalizations in mice selectively bred for high (NC900) and low (NC100) levels of aggression. Data are expressed as rate per minute (mean ± SEM).

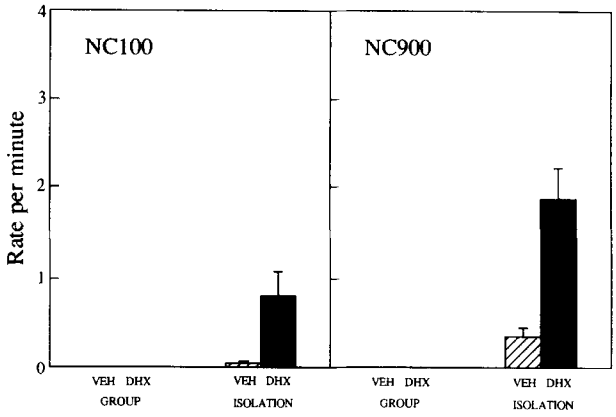

FIG. 6. Effects of rearing conditions (group, isolation) on dihydrexidine (DHX; 10 mg/kg)-induced increases in escape in mice selectively bred for high (NC900) and low (NC100) levels of aggression. Data are expressed as rate per minute (mean ± SEM).

Determination of D_1 Dopamine Receptor Function

It was hypothesized that differential effects of dihydrexidine across selected lines and rearing conditions would be reflected in correlated differences in D_1 dopamine receptor density. The densities measured in each case across six replicate experiments for each line are presented in Table 2. This table shows that for NC100 mice, isolated animals did not have significantly higher D_1 receptor densities than group-reared animals, $t(10) = 0.75$, exhibiting a mean increase in density of 6.4%. By contrast, for the NC900 line, significantly higher densities were observed in the isolation condition, $t(10) = 2.56$, $p < 0.05$. Across the six independent experiments, isolated NC900 mice exhibited a 20% increase in D_1 receptor density. As expected, no effect of selected line or rearing condition was found for affinity. The mean K_d was 0.31 and 0.32 for grouped and isolated NC900 mice, respectively, and 0.28 for both grouped and isolated NC100 mice (Table 2).

DISCUSSION

In a previous study (11), it was demonstrated that isolated high- and low-aggressive mice administered the full efficacy D_1 dopamine agonist, dihydrexidine, prior to a social interaction test, exhibited unusually high levels of reactivity when mildly stimulated by the partner mouse. This reactivity was substantially higher than that observed among isolated control animals. Moreover, this effect could be blocked by pretreatment with a selective D_1, but not a D_2, dopamine antagonist. These results suggested that D_1 dopamine receptors play an important, and heretofore unrecognized, role in the emotional response of organisms to novel environmental (social) stimuli. In the present study, it was hypothesized that isolation-induced reactivity may be mediated, at least in part, by an increase in the sensitivity of D_1 dopamine receptors. This hypothesis was examined by contrasting the effects of dihydrexidine among high- and low-aggressive mice that had been reared either singly or in groups prior to being exposed to an unfamiliar mouse. A further test of this hypothesis involved a direct comparison of D_1 receptor densities across rearing conditions, using radioligand binding techniques.

As expected, isolated control animals of the two selected lines exhibited substantially higher levels of reactivity to the

TABLE 2

COMPARISON OF STRIATA/D_1 DOPAMINE RECEPTOR FUNCTION BETWEEN HIGH- AND LOW-AGGRESSIVE MICE REARED IN ISOLATION AND SOCIAL GROUPS

	NC100					NC900				
	Group		Isolation			Group		Isolation		
	B_{max}	K_d	B_{max}	K_d	% Incr.	B_{max}	K_d	B_{max}	K_d	% Incr.
Mean*	74.98	0.28	80.92	0.28	6.40	72.73	0.31	91.18	0.32	20.00
SEM	5.0	0.01	6.2	0.01		5.77	0.05	4.31	0.04	

*Average of six Scatchard analyses per line per housing condition.

mild social stimulation provided by the partner mouse than did group-reared control animals. The effects of dihydrexidine on the social interactions of isolated animals were essentially the same as those observed in our previous study with these selected lines. In both cases, the rates of reflexive kicking, vocalizations, and jumps were significantly higher than those measured for similarly isolated, but vehicle-treated animals. Also replicated were the disruptive effects of this reactivity on the usually high frequencies of attacks in NC900 mice and nonagonistic approaches in NC100 mice, both of which were markedly reduced as a result of the drug treatment.

A critical test of our hypothesis involved verifying the significance of the interaction between drug treatment and rearing condition for all indices of social reactivity. As expected, for the three indexes submitted to analysis (kick, vocalization, and escape) dihydrexidine induced higher levels of reactivity among isolated than group-reared animals. For the most part, these interactions were verified only in the high-aggressive line. This was the case for both vocalization and escape. In this regard, the absence of a significant interaction for reflexive kicking probably reflects the fact that this index of social reactivity is more characteristic of the low-aggressive than the high aggressive line and that somewhat lower levels of reactivity following isolation are generally observed in the low aggressive line (6,8,11). Thus, the differential effects of dihydrexidine on social reactivity across line and rearing condition supported the hypothesis that the effects of isolation are mediated, at least in part, by an increase in the sensitivity of D_1 dopamine receptors. These findings further indicated that the effects of isolation are themselves dependent upon constraints imposed by differences in genetic background and/or developmental trajectory.

Relative to the group condition, the analysis of homogenate binding data revealed a significant increase in striatal densities of D_1 dopamine receptors among animals reared in isolation. The fact that such an increase was observed in the striatum is entirely consistent with the known functions of this area in the integration of affective and motivational states (13). Increased D_1 receptor densities in this area would explain the strong propensity among animals that have been reared in isolation to react strongly to the novel social stimulation provided by an unfamiliar animal. It would also explain the potentiated response to dihydrexidine observed in isolated animals. How much social reactivity is captured by our measure (i.e., in the first 2 min of interactions or prior to an agonistic action) is naturally dependent upon the timing of the first agonistic action, and by the fact that highly reactive animals tend to be attacked more rapidly. In this respect, the line differences observed in the present research in both levels and forms of reactivity were not as large as those measured in the preceding two generations. However, if not entirely supported by significant behavioral line differences, the significantly greater increase in D_1 receptor density observed in NC900 mice in the present study is entirely consistent with their known tendency to be more reactive to social stimuli following isolation than NC100 mice.

Studies of social/emotional behavior in both humans and animals have suggested that there are individual differences in temperament that appear early in development and constitute stable traits. Reactivity, particularly to novel stimuli, has been targeted as a fundamental dimension of temperament (9,14, 16). The present study suggests that individual differences in D_1 receptor function may mediate differential reactivity. Finally, our results indicate that D_1 receptor function, in addition to being constrained by genetic/maturational factors, is open to experientially induced changes.

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