Social Reactivity and D_1 Dopamine Receptors: Studies in Mice Selectively Bred for High and Low Levels of Aggression

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Robust individual differences in social behavior have been obtained by selectively breeding Institute for Cancer Research mice for high and low levels of aggression. As previously shown, when paired with a non-selected, group-housed partner mouse, NC900 mice exhibit isolation-induced aggression. Conversely, NC100 mice fail to attack, freezing upon social contact. Previous studies have established that NC100 mice have lower dopamine concentrations in nucleus accumbens and caudate nucleus, with increased dopamine receptor densities in these same regions. Thus, we wished to determine the effect of administration of a dopamine receptor agonist on social behavior. Mice of both lines were administered 0, 1, 3, or 10 mg/kg (SC) of the full efficacy D_1 receptor agonist dihydrexidine, and their behavior was assessed in a social interaction test. Dihydrexidine reduced aggression in NC900 mice and nonagonistic approach in NC100 mice in a dose dependent manner. In both cases, this resulted from induction of a marked reactivity to mild social stimulation as measured by increases in behaviors such as escape, reflexive kicking, and vocalizations. Dihydrexidine had no systematic effect on the freezing behavior characteristic of the low-aggressive line. In independent experiments, mice were pretreated with either the D_1 antagonist SCH-23390 (.1 mg/kg) or the selective D_2 antagonist remoxipride (1.0 mg/kg), after which they received dihydrexidine (10 mg/ kg) and were tested as above. The effects of dihydrexidine on social reactivity in mice of both lines were significantly antagonized by SCH-23390 but not attenuated by remoxipride. Antagonist pretreatment neither reinstated attack in the NC900 line nor non-agonistic approach behavior in the NC100 line, which suggests the importance of D_1/D_2 interactions to the initiation of action. These studies suggest an important role for D_1 dopamine receptors in the emotional response to social stimuli. [Neuropsychopharmacology 10:115–122, 1994]

Selective breeding has been a useful strategy in establishing lines of animals that originate from the same genetic background, but differ reliably in the expression of a specific behavioral trait. High or low levels of open-field activity, alcohol preference, "emotionality," and aggression are just some of the numerous behavioral characteristics that have been selectively bred with success (Fuller and Thompson 1978). The control of genetic background through selective breeding offers a useful technique for examining the neurobiological mechanisms that mediate the expression of specific behavioral traits. The same procedure also allows for examination of 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 twenty-fifth generation. This

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program was initiated by Cairns and his collaborators (Cairns et al. 1983) who selectively bred Institute for Cancer Research (ICR) mice for high or low levels of aggression. Line differences in attack appeared rapidly, with robust effects obtained by the fourth (S_4) generation (see also Lagerspetz 1964; van Ooortmerssen and Bakker 1981). Although designed as a bidirectional selective breeding experiment, relatively little change in attack across generations has been observed in the high-aggressive (NC900) line. Those mice (NC100) selected for low levels of aggression, however, have departed markedly from the S_0 generation, and now rarely exhibit the aggression expected of this mouse strain following individual housing. Rather, NC100 mice become inhibited in response to mild social contact, often exhibiting freezing following contact with an unselected male, ICR, group-housed, partner mouse.

The largely unidirectional outcome of the selective breeding program has been established in several key previous studies (Cairns et al. 1983), and observed in replicate lines (using sibling offspring starting in the S_{12} generation and identical assessment procedures) established at the Pennsylvania State University (Cairns et al. 1990). Although the criterion for selective breeding was male attack behavior, effects that parallel those obtained with males have been obtained with females in postpartum tests. High levels of postpartum aggression were observed in the NC900 line after successful line differentiation (i.e., S_6, S_7 and S_9), whereas NC100 females rarely attacked intruders during the postpartum period (Hood and Cairns 1988).

In the low-aggressive animals, the cross generational changes in attack behavior were paralleled by the development of freezing in response to mild social contact. The propensity to freeze in the high-aggressive animals did not deviate markedly from the foundational stock across generations, a result consistent with the unidirectional effects of selective breeding. Thus, one mechanism for the expression of the genetic change in aggression appeared to be the development of a behavioral response (freezing) incompatible with the sequence of behaviors leading to attack (Gariépy et al. 1988).

Previous studies have indicated that line differences in dopamine and dopamine receptor function may mediate some of the behavioral differences observed between the high and low aggressive lines (Lewis et al. 1988; DeVaud et al. 1989). Thus, in the experiments described below, we challenged both the high- and low-aggressive lines of mice with the direct-acting, full-efficacy D_1 agonist, dihydrexidine. Dihydrexidine has been shown to be several-fold more potent in radio-receptor assays than the prototypical D_1 agonist SKF-38393, and equally efficacious as dopamine in stimulating cyclic adenosine monophosphate synthesis in all preparations tested (Lovenberg et al. 1989; Brewster et

al. 1990; Watts et al. 1993). Dihydrexidine is approximately ten-fold selective for striatal D_1 vs. D_2 receptors, and is essentially devoid of other neurotransmitter receptor affinity (Mottola et al. 1992). Prior to administration of dihydrexidine in a second series of experiments, we treated mice from both lines with either a selective D_1 or D_2 antagonist to confirm the selectivity of the observed effects.

METHODS

Selection and Rearing

Attack behavior, observed only in males, was the sole criterion used in selectively breeding ICR mice (Mus musculus). The same criterion was employed in successive generations, and sisters of the selected males provided the mating partners for other males within each selected line. Brother–sister mating was not permitted. Earlier reports have detailed the breeding criteria, and the outcomes over successive early and late generations (Cairns et al. 1983; Gariépy et al. 1988). Male mice, in each generation, after weaning at 21 days of age, were reared in individual cages. They were tested at 45 days of age for aggressive behavior in social interaction tests. (This has been the standard test age for all previous generations.) They had no social contact other than exposure to the noises and odors produced in the colony room. The animals who served as test partners (NC600) were reared, after weaning, in groups of four males. The NC600 line was derived from the same foundational stock of animals that served to establish the selected lines of mice. The NC600 line, however, was propagated without selection throughout the research program. Details of these methods and housing procedures have been described previously (Cairns et al. 1983; Gariépy et al. 1988).

Social Interaction Test

In the social interaction test, each subject was placed on one side of the test cage, and a same-age, group-reared male of the unselected line (NC600) was placed on the other side. The test cage was constructed of Plexiglas ($20 \times 21 \times 31$ cm), with a removable sheet-metal panel dividing the compartment in two separate chambers. After five minutes, the panel was removed, and interactions between the subject and the partner were scored for 10 minutes. After testing, both animals were weighed and then returned to their home cages.

In the social interaction test, the behavior of both the test animal and the partner mouse was scored. This continuous scoring method allowed us to code: (a) the behavior of the test animal towards 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 ani-

Table 1. Behavioral Categories Coded in the Social Interaction Test

Behavioral Category	Definition
Freeze	Immobile and seemingly frozen, upon and following social stimulation
Escape	Rapid retreat, running away
Jump	Rapid upward movement with all four paws leaving the ground
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
Box Posture	Upright posture with front paws held close to the body
Hold	Use of the front paws to fend off or maintain other animal at a distance
Feint	Attack-like action not resulting in actual physical contact
Attack	Vigorous lunge toward the other animal with biting or slashing

mals, and, within-animal, autocorrelated behaviors and states (Cairns and Nakelski 1971; Cairns and Scholz 1973). For the several generations in which these behavioral categories have been used, inter-observer agreement has always exceeded 90%. All behavioral procedures were conducted with experimenters uninformed as to which selected lines were represented in the tests.

Dihydrexidine-Induced Behavior: Dose Effects

Mice of each line were injected (SC) with either vehicle, 1.0, 3.0, or 10.0 mg/kg of dihydrexidine (n = 12 per line per dose), 10 minutes prior to testing. The behaviors were scored as described above. Attack, freezing, and social initiations were expressed as the number of 5-second blocks in which the behavior occurred over the 10-minute test period. Behaviors indicative of reactivity (e.g., startle/withdrawal, vocalizations, reflective kicking, box-hold, jump, and escape) were scored as rate per minute. The frequency of these behaviors was calculated over the first 2 minutes of the social interaction or before the initiation of an agonistic action (e.g., feint, bit, 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 defeat (Cairns et al. 1985). Thus, rates per minute of preagonistic reactivity were calculated to permit comparisons across test sessions and disentangle drug effects from agonistic interaction effects. Frequency and rate per minute data were subjected to two–factor (2 × 4) analyses of variance (ANOVAs) to test for line, drug, and line-by-drug interactions.

Dihydrexidine-Induced Behavior: Effects of Selective Receptor Blockade

This study was conducted in a manner similar to the previous one except that drug- and experience-naive

animals were injected with either .1 mg/kg SCH-23390 (n = 8 per line) or 1.0 mg/kg remoxipride (n = 8 per line). Thirty minutes later, the animals in each condition were injected with 10 mg/kg dihydrexidine. Behaviors were scored and expressed as above. Data were subjected to similar ANOVAs to test for main effects and interactions.

RESULTS

Dihydrexidine-Induced Behavior: Dose Effects

The frequencies of both attack and freezing, as well as their latencies (data not shown), observed in vehicle-treated animals were essentially the same as those ob-
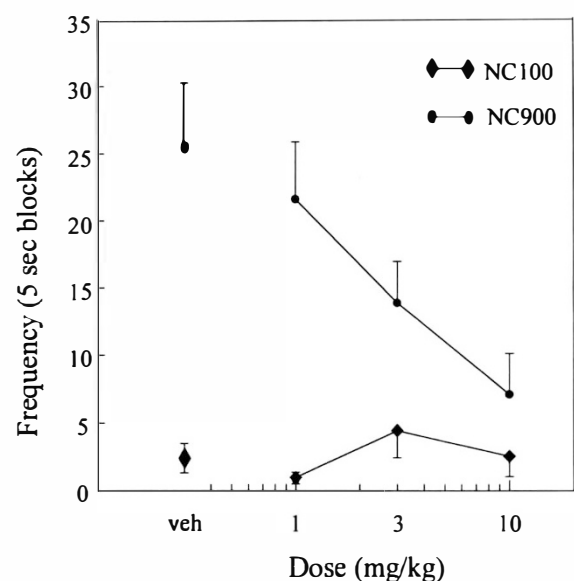

Figure 1. Dose-dependent effects of dihydrexidine on the frequency (number of 5-second intervals) of attacks in mice selectively bred for high (NC900) and low (NC100) levels of aggression.
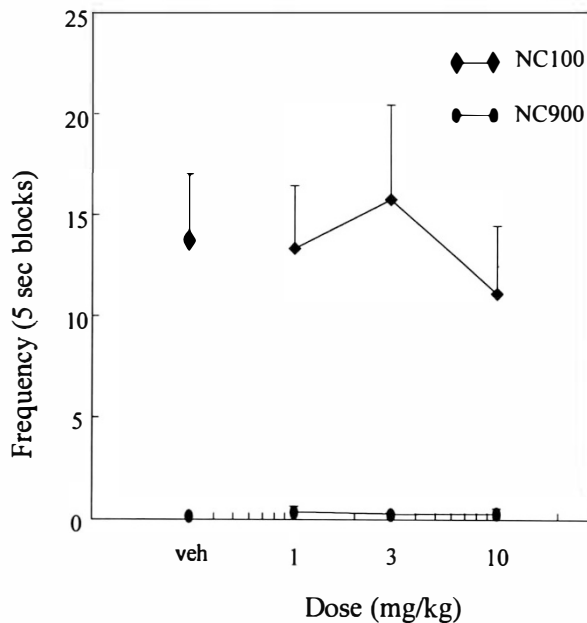
Figure 2. Dose-dependent effects of dihydrexidine on the frequency (number of 5-second intervals) of freezing in mice selectively bred for high (NC900) and low (NC100) levels of aggression.

Figure 3. Dose-dependent effects of dihydrexidine on the frequency (number of 5-second intervals) of non-agonistic approach behavior in mice selectively bred for high (NC900) and low (NC100) levels of aggression. This behavioral category was defined by the responses of sniffing the partner mouse, directed sniffing at its ano-genital region, and climbing on the partner mouse.

tained for noninjected controls of the same generation. Dihydrexidine reduced aggression in NC900 mice in a dose-dependent manner (Fig. 1) to the point that, at the highest dose, there was no statistically significant line difference in attack. No drug effect was observed on the very low levels of aggression exhibited by the NC100 mice. These effects were reflected in a statistically significant main effect for dose ($F[3,96] = 3.62, p = .02$), and in the line by dose interaction ($F[3,96] = 5.0, p = .003$).

Dihydrexidine had no systematic effect on the freezing behavior characteristic of the low-aggressive line (Figure 2). Although the expected significant line difference was obtained ($F[1,96] = 47.9, p = .000$), no dose effect ($F[3,96] = .3, p = .85$) or dose-by-line interaction ($F[3,96] = .3, p = .83$) was found.

Dihydrexidine did, however, have a substantial effect on the frequency of nonagonistic approach behaviors initiated by the target mouse toward its partner. These behaviors constituted mild social stimulation and typically involved sniffing the partner mouse, with sniffing directed at its ano-genital region, and climbing on the partner mouse. As expected from studies of non-treated animals of previous generations, NC100 mice exhibited significantly higher frequencies of this behavior across all doses tested than NC900 mice ($F[1,48] = 46.2, p < .000$). The effect of the drug, however, was to dose-dependently decrease these behaviors in NC100 mice ($F[1,48] = 13.0, p = .001$), while having
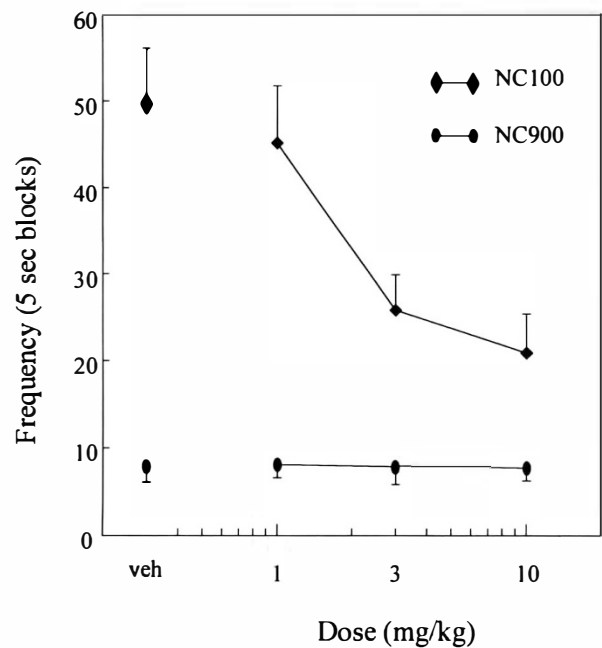
no effect on the low frequencies that were observed in NC900 mice. These results are presented in Figure 3.

The decrease in attack behavior observed in the NC900 line and the decrease in nonagonistic approach behavior in the NC100 line were dose-dependently related to an increase in the reactivity of these mice to the mild social stimulation provided by the partner. Reactivity, as it is observed in the social interaction test, is expressed as two clusters of behaviors. The first cluster, defined by factor analyses, consists of the following behavioral categories: startle/withdrawal (W), reflexive kicking (K), vocalizations (V), and box-hold (BH). The second group of related behaviors identified by this analysis was a cluster made up of the categories jump (J) and escape (E). Typically, low-aggressive mice tend to exhibit somewhat higher rates of the first cluster (WKVBH), whereas high-aggressive mice tend to show higher rates of the second cluster (JE).

Figure 4 shows that this tendency toward a line difference in type of reactivity was present in the social behavior of animals treated with vehicle. As expected, a significant main effect for line was found for WKVBH ($F[1,96] = 7.1, p = .01$) with higher rates observed in NC100 mice. A significant drug effect was also found ($F[3,96] = 5.2, p = .002$) with no evidence of a drug-by-line interaction ($F[3,96] = .7, p = .54$). As depicted in
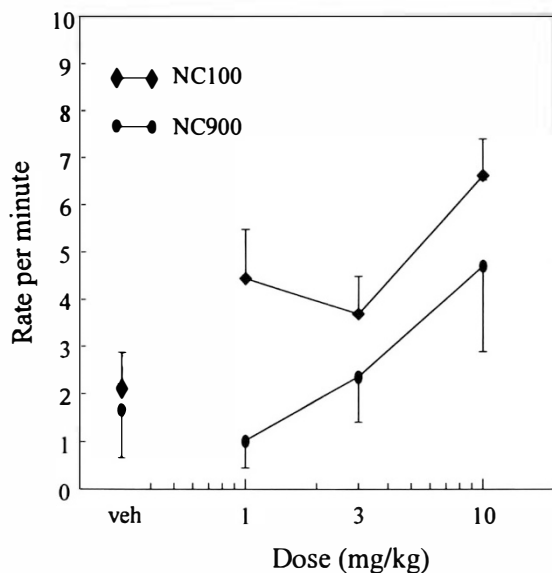
Figure 4. Dose-dependent effects of dihydrexidine on the frequency (number of 5-second intervals) of social reactivity in mice selectively bred for high (NC900) and low (NC100) levels of aggression. In this case, social reactivity is the composite of the behaviors withdraw, kick, vocalize, box-hold.

Figure 4, a significant increase in reactivity was observed in both lines, largely due to effects observed at the highest dose. An analysis of each behavioral component of this form of reactivity showed that dihydrexidine significantly increased the rate of reflexive kicking, vocalizing, and box-hold. The rate of startle-withdrawal
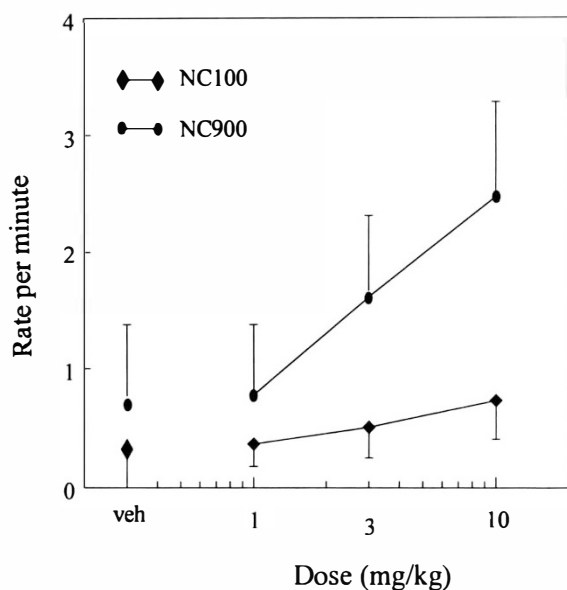

Figure 5. Dose-dependent effects of dihydrexidine on the frequency (number of 5-second intervals) of escape in mice selectively bred for high (NC900) and low (NC100) levels of aggression. Data are expressed as rate per minute.

was quite low across all conditions and, hence, not subjected to individual analysis.

The analysis conducted separately for the second cluster of reactive behaviors (JE) also revealed the expected line difference with higher rates observed in the NC900 line ($F[1,96] = 7.9$, $p = .01$). No drug effect was observed, however, ($F[3,96] = .5$, $p = .68$), and there was no line by drug interaction ($F[3,96] = .3$, $p = .86$). The same pattern was observed when jump and escape were analyzed independently. The rate of escape behaviors was significantly greater in the highest dihydrexidine dose when compared to vehicle, however. This result is depicted in Figure 5.

As expected, NC100 mice also showed a substantially shorter latency to exhibit reactivity (WKVBH) than NC900 mice ($F[1,96] = 24.2$, $p = .000$). This latency was significantly decreased by dihydrexidine ($F[3,96] = 3.2$, $p = .03$), but not differentially across the two lines $F[3,96] = .8$, $p = .48$). Although dihydrexidine did not significantly affect the rate of jump-escape (JE) in either line, it did significantly decrease the latency to JE ($F[3,96] = 4.7$, $p = .004$) in both groups.

Dihydrexidine-Induced Behavior: Effects of Selective Receptor Blockade

In independent experiments, mice of both lines were pretreated with either the selective D_1 antagonist SCH-23390 (.1 mg/kg) or the selective D_2 antagonist remoxipride (1.0 mg/kg), after which they received dihydrexidine (10 mg/kg) and were tested as above. In replication of the previous experiment, administration of 10 mg/kg of dihydrexidine abolished the robust line difference in attack behavior ($F[1,31] = 1.6$, $p = .21$). Of note was the fact that pretreatment with neither the selective D_1 antagonist SCH-23390, nor the selective D_2 antagonist remoxipride reversed the effects of dihydrexidine or attack. Similarly, no effect of drug pretreatment was seen on the dihydrexidine-induced decrease in nonagonistic approach behavior observed in low-aggressive mice.

The effects of 10 mg/kg of dihydrexidine on reactivity as defined by the behaviors withdraw, kick, vocalize, box-hold (WKVBH) were significantly affected by drug pretreatment ($F[1,31] = 4.1$, $p = .05$). As seen in Figure 6, animals pretreated with SCH-23390 exhibited significantly less dihydrexidine-induced reactivity than those pretreated with remoxipride. This effect was particularly obvious in low-aggressive mice, although no statistically significant drug-by-line interaction was found ($F[1,31] = 1.1$, $p = .31$). It should be noted that the rates of WKVBH induced by dihydrexidine in this experiment closely paralleled those obtained in the previous experiment (see Figure 4). It should also be noted that SCH-23390 pretreatment returned WKVBH
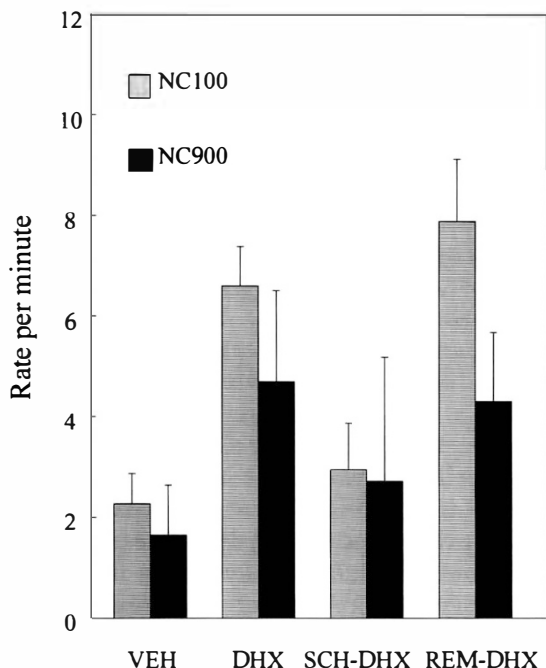
Figure 6. Effects of pretreatment with a selective D_1 (.1 mg/kg SCH-23390) or D_2 (1.0 mg/kg remoxipride) antagonist on dihydrexidine (10 mg/kg)-induced increases in social reactivity (withdraw, kick, vocalize, box-hold). Data are expressed as rate per minute.
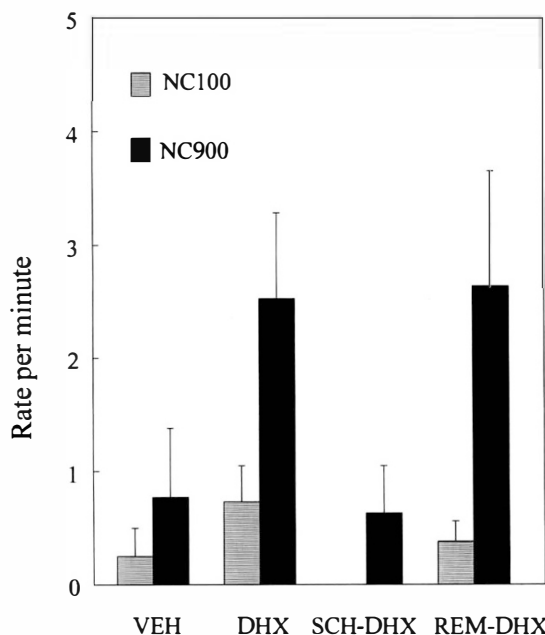

Figure 7. Effects of pretreatment with a selective D_1 (.1 mg/kg SCH-23390) or D_2 (1.0 mg/kg remoxipride) antagonist on dihydrexidine (10 mg/kg)-induced increases in escape. Data are expressed as rate per minute.

rates to those observed in vehicle-treated mice. There was no effect of drug pretreatment on the latency to WKVBH.

As described above, when compared to vehicle, the highest dose of dihydrexidine increased escape rates. Drug pretreatment had a significant effect on the rate of escape induced by this same dose of dihydrexidine ($F[1,31] = 4.6$, $p = .04$). As seen in Figure 7, pretreatment with SCH-23390 decreased escape in both lines to rates lower than those observed in vehicle-treated mice of each respective line. No effect of pretreatment was observed on rates of jump. The latency to jump-escape following dihydrexidine was significantly affected by drug pretreatment ($F[1,31] = 10.4$, $p = .003$) with SCH-23390-treated mice exhibiting significantly higher latencies than remoxipride-treated mice.

DISCUSSION

The full efficacy D_1 dopamine agonist, dihydrexidine, induced a marked reactivity in both selected lines in response to the mild social stimulation provided by a partner mouse. This reactivity interfered with the attack behavior typical of the NC900 line such that, at the highest dose of dihydrexidine, no difference in aggression was observed between the two lines. Dihydrexidine also disrupted the nonagonist approach behavior seen in NC100 mice, but was found to have no effect at all on the freezing behavior of this line. The effect of dihydrexidine on reactivity to mild social stimulation was measured by the significant increase observed after drug administration in the rates of withdrawal, reflexive kicks, vocalizations, and the defensive posture box-hold. Dihydrexidine did not affect a second form of reactivity defined by the behaviors jump and escape, although the rate of escape behavior was significantly greater in mice administrated the highest dose of dihydrexidine relative to mice given vehicle. Pretreatment with the D_1 antagonist SCH-23390 (.1 mg/kg), but not the D_2 antagonist remoxipride (1.0 mg/kg), blocked the induction of social reactivity (WKVBH) by dihydrexidine. This effect was not associated with a significant reemergence of aggressive behavior, however. SCH-23390 pretreatment was associated with a decrease in the rate of escape to below that observed in vehicle-treated mice.

The effects of dihydrexidine on social reactivity could only be considered robust at the 10 mg/kg dose. At this dose, it may be that dihydrexidine also interacts with at least some populations of D_2-like receptors (Darney et al. 1991; Mottola et al. 1992). If such an action were involved in the behavioral effects observed, blockade of these receptors by the D_2 antagonist remoxipride should have an effect on social reactivity. Little evidence for this effect was found, however. Thus,

our findings support the conclusion that reactivity to social stimulation in mice appears to be mediated, at least in part, by D_1 but not D_2, dopamine receptors. If such a conclusion is warranted, these will be among the first data to point to an important role for D_1 dopamine receptors in the emotional response to social or other environmental stimulation.

Preliminary data gathered in independent experiments by our group (Schmitt et al. 1992) suggest that D_1 receptors also play a role in mediating the emotional response to non-social stimuli. In these experiments, dihydrexidine injected intracerebrally into nucleus accumbens of rats induced a hyperreactive response to both auditory and tactile stimulation. The availability of a full-efficacy D_1 agonist has permitted this new information concerning the functional roles of D_1 dopamine receptors to be obtained. Whereas species comparisons required great caution, it may be that D_1 dopamine receptors play a role in emotional responding in humans. 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 (Suomi 1987; Kagan et al. 1988; Rothbart 1988). Whether genetic or early-experience–induced differences in D_1 receptor function are important mediators of such temperament differences remains to be established.

Our findings also provide evidence for an important relationship between reactivity and aggression (Gariépy et al. 1988). Consistent with the observation that heightened reactivity is incompatible with attack, we have noted anecdotally in drug-naive animals tested in previous generations that those NC900 mice that exhibit the highest levels of reactivity display little attack.

Two observations from the SCH-23390 antagonist pretreatment study were not consistent with direct action at only D_1 receptors. First, SCH-23390 decreased the dihydrexidine-induced escape behavior to below the rate observed in vehicle-treated animals; and second, after blockade by SCH-23390 of the dihydrexidine-induced social reactivity, there was neither a reinstatement of attack in NC900 mice nor non-agonistic approach behavior in NC100 mice. The D_1 antagonist SCH-23390 has been shown to inhibit potently apomorphine-induced stereotyped behavior and amphetamine-induced locomotion, behaviors that were once believed to be largely or exclusively D_2 receptor mediated (Mailman et al. 1984). The importance of D_1/D_2 receptor interactions in the expression of a variety of behaviors is now widely appreciated (Braun and Chase 1986; Mashurano and Waddington 1986; Arnt et al. 1987; Meller et al. 1988; Brodi and Meller 1989). It may be that SCH-23390 administration affected behaviors (escape, attack, social approach), the initiation of which are dependent on the coactivation of both D_1 and D_2 receptors.

The present findings suggest that D_1 dopamine receptors appear to play an important, and heretofore unrecognized, role in the emotional reaction of the organism to environmental (social) stimuli. Activation of D_1 receptors caused treated mice to respond to mild social stimulation by withdrawal, reflexive kicking, and vocalizations, effects blocked by a D_1 but not a D_2 antagonist. It is tempting to speculate on the anatomical basis of this effect. Certainly, the amygdala should be an important candidate. The amygdala has been shown to contain "D_1-like" receptors, albeit ones not linked to adenylate cyclase (Kilts et al. 1988; Mailman et al. 1986a, 1986b), and there is a wealth of data implicating the amygdala in the mediation of fear-related responding. Several lines of evidence support an important role for basal ganglia dopamine in the motivational state of an organism and its ability to initiate adaptive behavioral responses rapidly (Kelly et al. 1982; Nabeshima et al. 1986). Louilot et al. (1986) have proposed that dopamine plays a key role in the integration of affective, emotional, and motivational states with the initiation of action. More specifically, it has been proposed that striatal and nucleus accumbens dopamine is important in how neocortical and limbic (e.g., amygdala) areas influence complex motor behavior. Although delineation of the chemoarchitecture related to these findings is necessary, the present study indicates that D_1 dopamine receptors play a critical and unexpected role.

ACKNOWLEDGMENTS

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