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Individual differences in behavior following amphetamine, GBR-12909, or apomorphine but not SKF-38393 or quinpirole

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Abstract. Subjects that respond more to a novel environment show a greater locomotor response to drugs of abuse such as cocaine and amphetamine. The current study was performed to examine differences between high (HR) and low (LR) responding rats to a novel environment following administration of amphetamine, a selective dopamine uptake blocker (GBR-12909), a nonselective dopamine agonist (apomorphine), and selective dopamine D_1 and D_2/D_3 agonists. A behavioral checklist and a rating scale were used to determine the behavioral arousal caused by administration of amphetamine (0, 0.5, 2.0, and 8.0 mg/kg), GBR-12909 (0, 1.25, 5.0, and 20.0 mg/kg), apomorphine (0, 0.1, 0.3, and 1 mg/kg), SKF 38393 (0, 2.5, 10, and 40 mg/kg), or quinpirole (0, 0.05, 0.5, and 5.0 mg/kg). The five drugs produced behavioral activation profiles distinct from each other. Following amphetamine administration, both HR and LR subjects showed dose dependent increases in behavioral arousal. The behaviors primarily affected were sniffing, locomotor activity, rearing, and oral activity. HR rats showed a greater overall behavioral response to amphetamine administration compared with LR rats and there were differences in specific behaviors between the two groups. Following GBR-12909 administration, all subjects showed dose dependent increases in sniffing, locomotor activity, and rearing. Differences between HR and LR were observed in sniffing, locomotor activity, and rearing behaviors. HR and LR both showed dose dependent increases in behavior following apomorphine administration. HR showed greater behavioral activation after apomorphine than LR. SKF 38393 produced pronounced increases in the amount of sniffing, grooming, and intense grooming, in addition to increasing the overall behavioral rating of all subjects, while quinpirole produced increases in sniffing, locomotor activity, and oral movements. However, the behavioral effects of SKF 38393 and quinpirole did not differ between HR and LR. These results suggest that activation of the dopamine system but probably not only one type of dopamine receptor is sufficient to produce behavioral differences between high and low responding subjects.

Key words: Individual differences – Novelty – Amphetamine – Apomorphine – SKF 38393 – Quinpirole – Dopamine receptors – GBR-12909

Subjects that show a greater locomotor response to a novel environment (high responders; HR) acquire amphetamine self-administration more readily (Piazza et al. 1989), sensitize more readily to repeated amphetamine administration (Hooks et al. 1991a, 1992a,b), and show a greater locomotor response to acutely administered amphetamine and cocaine (Hooks et al. 1991a,b, 1992a,b,c) than subjects that show less of a locomotor response to novelty (low responders; LR). Both amphetamine and cocaine exert their motor stimulant effects through the dopaminergic system (Kelly and Iversen 1976). Therefore, it is not surprising that HR show a greater dopaminergic response to amphetamine and cocaine administration than LR (Hooks et al. 1991b,c). In addition, there are basal differences in both tissue (Piazza et al. 1991) and extracellular dopamine levels between HR and LR subjects (Hooks et al. 1992c).

Recent evidence has suggested (Hooks et al. 1993) that variation in the population of dopamine receptors may contribute to the differences between HR and LR rats. HR have about 50% fewer dopamine D_2 receptors in the nucleus accumbens and striatum than LR. Differences in dopamine D_1 receptors also exist, but are smaller (only about 20%) and only in the nucleus accumbens. The differences between HR and LR may be analogous to those seen between drug-sensitized and naive subjects. Sensitized subjects, like HR, show a heightened behavioral

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response to amphetamine and cocaine (Hooks et al. 1992a,c). In addition, repeated administration of cocaine or amphetamine has been shown to alter the number of dopamine D_1 and D_2 binding sites in the striatum and nucleus accumbens (Nielsen et al. 1983; Goeders and Kuhar 1987; Kleven et al. 1990; Farfel et al. 1992), resulting in differences between sensitized and naive rats that are similar to the differences observed between HR and LR.

Other studies have shown that compared with control subjects, subjects that are chronically exposed to stress or drugs of abuse differ in their behavioral response to selective dopamine agonists (Sharp et al. 1990; Ujike et al. 1990). For example, subjects that are exposed to repeated electroconvulsive shock (ECS) show an increased behavioral response to the D_1 agonist SKF 38393, but not to the D_2 agonist RU 24213 (Sharp et al. 1990). In contrast, subjects repeatedly exposed to methamphetamine or cocaine show an augmented behavioral response to the D_2/D_3 agonists quinpirole and RU 24213, but not to the D_1 agonist SKF 38393 (Ujike et al. 1990). This indicates that either D_1 or D_2/D_3 receptor activation may be responsible for differences in behavioral activation in sensitized subjects.

In order to investigate the role that dopamine D_1 or D_2/D_3 receptors might have in mediating the differences that exist between HR and LR, the present study assessed the unconditioned behavioral effects induced by the dopamine releaser amphetamine, the selective dopamine uptake inhibitor GBR 12909, the nonselective dopamine agonist apomorphine, the D_1 agonist SKF-38393, and the D_2/D_3 agonist quinpirole using a behavioral checklist technique and behavioral rating scale (Fray et al. 1980; Molloy and Waddington 1987).

Materials and methods

Subjects. Eighty-four male Sprague Dawley rats (Harlan) aged 60–90 days old and weighing approximately 290–340 g at the start of the study were used. Animals were housed three per cage with free access to food and water under a 12-h light/dark cycle (lights on from 0700 to 1900 hours). Testing was performed between 0800 and 1500 hours. Amphetamine, SKF 38393 and quinpirole drug treatment groups were composed of 20 subjects (HR, $n = 10$; LR, $n = 10$). The GBR-12909 and apomorphine drug treatment groups were composed of 12 subjects (HR, $n = 6$; LR, $n = 6$).

Drugs. Amphetamine sulfate (Sigma Inc.), apomorphine (Research Biochemicals Inc.), and quinpirole hydrochloride (Research Biochemicals Inc.) were dissolved in saline and administered subcutaneously in a volume of 1 ml/kg. SKF 38393 hydrochloride (Research Biochemicals Inc.) was dissolved in distilled sterile water and administered in a volume of 2 ml/kg subcutaneously. GBR-12909 dihydrochloride (Research Biochemicals Inc.) was dissolved in hot isotonic saline with 4 mg/ml tartaric acid and administered IP in a volume of 1 ml/kg.

Response to novelty. Subjects were placed in individual photocell cages for a 1-h period and were divided into HR and LR based on whether their locomotor activity scores for the hour were in the upper half or lower half for the population screened (Hooks et al. 1991a). This results in HR having about a 50% higher locomotor level in the novel environment compared with LR.

Behavioral measurement. Behavioral responses induced by injection of amphetamine, GBR-12909, apomorphine, SKF 38393, and quinpirole were assessed in individual rats. The behavioral rater was unaware of the subject's novelty response and dose of drug.

Three days after subjects were screened for novelty response, they were placed in individual, clear, perspex cages and allowed to habituate for 3 h. Three days following the habituation session drug testing commenced. Subjects received one of five drugs, amphetamine (vehicle, 0.5, 2.0, and 8.0 mg/kg), GBR-12909 (vehicle, 1.25, 5.0, 20.0), apomorphine (vehicle, 0.1, 0.3, and 1 mg/kg), SKF 38393 (vehicle, 2.5, 10.0, and 40.0 mg/kg), or quinpirole (vehicle, 0.05, 0.5, and 5.0 mg/kg), in a Latin-square design. A 72-h period separated the administration of each dose similar to a previous experiment (Ujike et al. 1990).

Subjects were allowed a 1.5-h period to habituate to the test cages prior to each drug challenge. Individual components of behavior were assessed using a modification of the methods of Molloy and Waddington (1987) and Sharp et al. (1990). A rapid-time sampling behavioral checklist technique and rating scales were used to measure drug induced behavior. Subjects were scored immediately before and for a 1-h period after drug administration. For the behavioral checklist technique, each rat was observed for a 10-s period at 5-min intervals over the 1-h period following drug administration. Subjects were scored for the presence or absence of six behaviors (Fray et al. 1980; Sharp et al. 1990); sniffing (sniffing for at least 3 s of the 10-s period), locomotor activity (all four limbs moved to a new position), rearing (both front feet off the cage floor), grooming (grooming of the snout with the forepaws), intense grooming (forepaw grooming of the snout followed by intense grooming of the hind flank with the snout), and oral (chewing, licking, and/or biting). For the 1 h after drug administration observation cycles were repeated at 5-min intervals for a total of 12 scoring periods.

Overall behavior was rated on a 0 to 6 point scale for amphetamine or 0 to 4 point scale for SKF 38393, quinpirole, apomorphine, and GBR-12909 immediately after behavioral checklist scoring. These scales were different for all five drugs. For amphetamine the rating scale was as follows: 0, asleep/inactive; 1, intermittent locomotor activity; 2, continuous locomotor activity with stereotyped sniffing and rearing; 3, stereotyped behavior maintained over a wide range of the cage; 4, continuous stereotypy in a restricted area of the cage; 5, continuous stereotyped behavior in a restricted location with licking at the walls or floor; 6, continuous stereotyped behavior in a restricted location with biting (Creese and Iversen 1973). For GBR-12909 the rating scale was as follows: 0, asleep/inactive; 1, sporadic locomotor activity with some sniffing; 2, intermittent locomotor activity; 3, continuous slow locomotor activity; 4, continuous rapid locomotor activity. For apomorphine the rating scale was as follows: 0, asleep/inactive; 1, sporadic locomotor activity with some sniffing; 2, intermittent locomotor activity with sniffing and rearing; 3, unfocused stereotypic sniffing and/or oral activity with some motor activity; 4, focused stereotypic sniffing and/or oral activity. For SKF 38393 the rating scale was as follows: 0, asleep/inactive; 1, occasional sniffing; 2, periodic locomotion with occasional sniffing or grooming; 3, frequent bursts of grooming of the snout and hindflank; 4, continuous on-the-spot grooming (Sharp et al. 1990). For quinpirole the rating scale was as follows: 0, asleep/inactive; 1, periodic sniffing or periodic oral movements; 2, repetitive sniffing with oral movements; 3, continuous sniffing with occasional locomotion or oral movements; 4, intense locomotion interspersed with prominent sniffing and grooming or continuous on the spot oral movements. Five distinct rating scales were used because of the differing behavioral arousal profiles of the five drugs.

Data analysis. The checklist data were analyzed by arranging the data in contingency tables. For each response category, at each dose level, novelty group, and for each 5-min interval, the number of rats out of ten or six showing, as well as those not showing, a particular category were calculated. Thus each table consisted of eight rows and two columns. As has been previously described, each degree of heterogeneity in each contingency table was then calculated by a likelihood ratio method, the 'information statistic' (Kullback 1968;

Robbins 1977; Fray et al. 1980). Each of the 12 time intervals for each behavioral score was analyzed separately. Groups were then analyzed as previously described (Kullback 1968; Robbins 1977; Fray et al. 1980). Groups were determined significantly different if they were at the 5% significance level. The behavioral rating data was analyzed similarly except an 8 × 7 or 8 × 5 matrix was used dependent on whether a 6- or 4-point rating scale was used. The median for the 12 observations was used for statistical and graphic purposes.

Results

Response to amphetamine

For both HR and LR rats amphetamine produced behavioral activation at all doses tested (Fig. 1A). This activation was highly dose dependent as the 8 mg/kg dose produced greater behavioral activation than any of the other doses tested. The 2 mg/kg dose also produced greater behavioral activation than vehicle or the 0.5 mg/kg dose. Figure 2 shows that sniffing was increased by all doses tested. Locomotor activity was also elevated by the 0.5 and 2.0 mg/kg doses (Fig. 3). Figure 4 demonstrates that rearing was enhanced by all doses of amphetamine with the 2.0 mg/kg dose producing the most rearing. Oral activity was also enhanced by amphetamine but only following the highest dose (Fig. 5). Grooming and intense grooming were not significantly altered by amphetamine (data not shown).

When HR and LR rats were compared, HR had a greater level of behavioral activation than LR at all doses tested (Fig. 1A). HR also showed a greater occurrence of locomotor activity compared with LR following both the 0.5 and 2 mg/kg doses (Fig. 3). As can be seen in Fig. 3, this was primarily in the 40 min after amphetamine injection. Rearing was greater in HR in the 20 min after 0.5 mg/kg amphetamine and lower in minutes 15–60 after 8 mg/kg (Fig. 4) compared with LR. Oral activity was greater in HR in minutes 25–60 compared with LR following the 8 mg/kg dose (Fig. 5). There were no differences between HR and LR rats for the other observed behaviors. Vehicle treatment did not produce any differences between HR and LR in any of the activities monitored.

Behavioral response to the selective dopamine uptake blocker GBR-12909

When HR and LR were analyzed as one group, GBR-12909 produced dose-dependent behavioral activation at all doses tested (Fig. 1). This is evident in the behavioral rating as all doses of GBR-12909 produced an increased behavioral rating score compared with vehicle treatment.

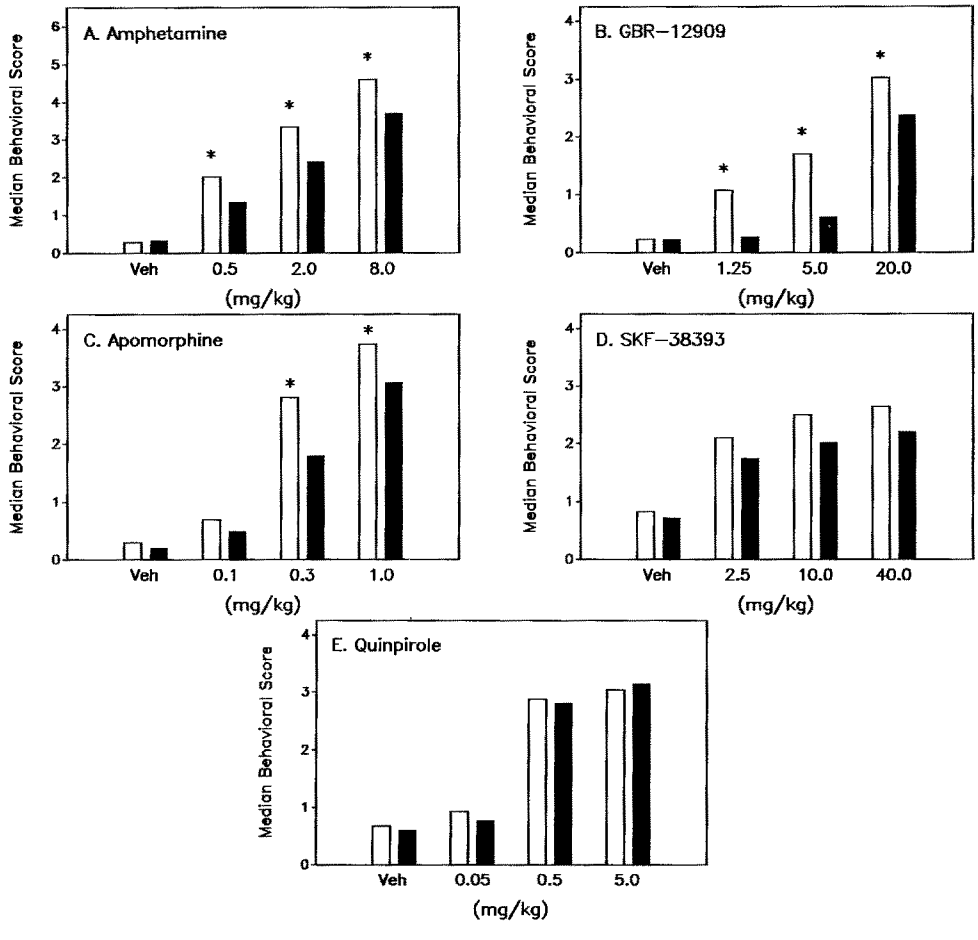

Fig. 1A–E. Median behavioral rating score for the 1 h following administration of amphetamine, GBR-12909, apomorphine, SKF-38393, or quinpirole. *Dark bars* represent LR while *open bars* represent HR. $*P < 0.05$, HR compared with LR

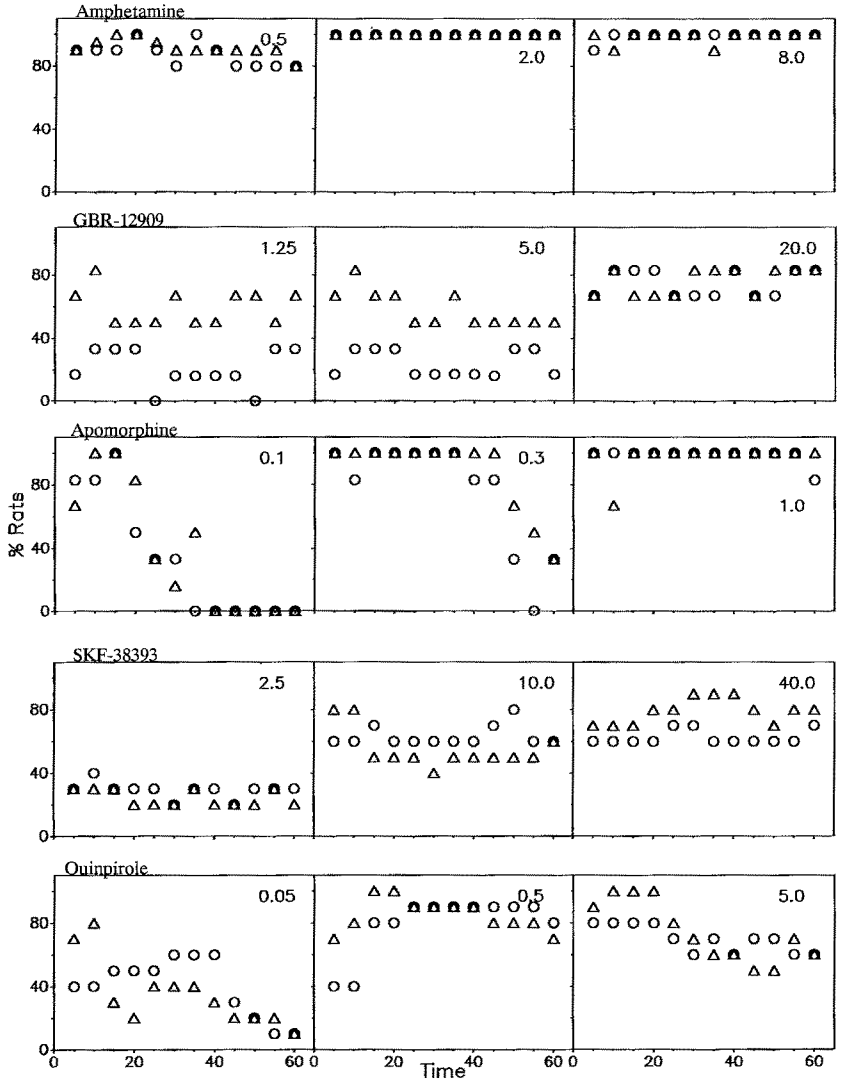

Fig. 2. Percentage of rats displaying sniffing following amphetamine, GBR-12909, apomorphine, SKF-38393, or quinpirole. The dose of drug expressed in mg/kg is in the *upper right corner* of each graph. ○, LR; △, HR

The 20 mg/kg dose produced greater behavioral activation than any other treatments. The 5 mg/kg dose also produced greater behavioral activation than the 1.25 mg/kg dose or vehicle. Sniffing (Fig. 2) was significantly increased at all doses tested. Similar to the behavioral rating, the 20 mg/kg dose produced greater behavioral activation than any other treatments. The 5 and 1.25 mg/kg doses also produced greater behavioral activation than the vehicle. Locomotor activity (Fig. 3) was also increased by GBR-12909 administration, while all doses tested significantly elevated locomotor activity compared with vehicle. The 20 mg/kg dose produced a significant increase in locomotor activity compared to the lower doses. Subjects exhibited a dose dependent increase in rearing behavior (Fig. 4). All doses tested elevated rearing compared with vehicle treatment, but the 20 mg/kg dose elevated rearing greater than any of the lower doses. None of the other behaviors was significantly altered by GBR-12909 treatment.

When HR and LR were compared, LR had lower behavioral scores compared with HR for all doses tested (Fig. 1B). For the individual components of behavior there were differences between HR and LR in sniffing, locomotor activity, and rearing. Sniffing was enhanced in HR compared with LR across the entire test period following both the 1.25 and 5.0 mg/kg doses (Fig 2). Locomotor activity was enhanced in HR compared with LR following all doses (Fig. 3). This was over nearly the entire timecourse for all doses. Rearing was significantly decreased in HR compared with LR following the 20 mg/kg dose in the middle portion of the time course. There were no differences between HR and LR rats for the other observed behaviors. Vehicle treatment did not produce any differences between HR and LR in any of the activities monitored (data not shown).

Behavioral response to the nonselective dopamine agonist apomorphine

When HR and LR were analyzed as one group, apomorphine produced dose dependent behavioral activation at the highest two doses tested (Fig. 1C). The 1.0 mg/kg dose produced greater behavioral activation than any other treatments. The 0.3 mg/kg dose also produced greater behavioral activation than the 0.1 mg/kg dose or

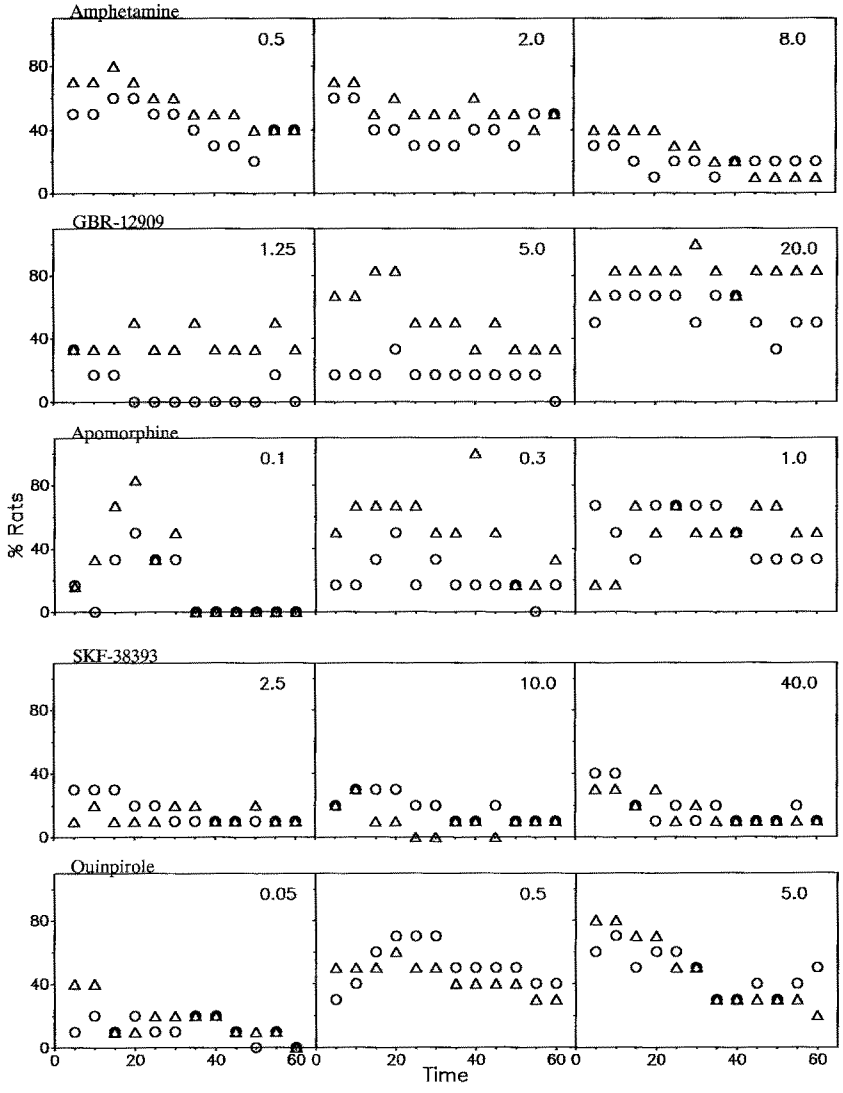

Fig. 3. Percentage of rats displaying locomotor activity following amphetamine, GBR-12909, apomorphine, SKF-38393, or quinpirole. The dose of drug expressed in mg/kg is in the *upper right corner* of each graph. ○, LR; △, HR

vehicle. Sniffing (Fig. 2) was significantly increased at all doses tested. Locomotor activity (Fig. 3) was also increased by apomorphine administration. All doses tested produced a significant elevation of locomotor activity compared with vehicle in the initial 30 min following drug treatment. The 1 mg/kg dose produced a significant elevation in locomotor activity compared to the lower doses in the later 30 min of testing. Subjects also exhibited dose-dependent differences in rearing behavior (Fig. 4). The two highest doses tested elevated rearing compared with vehicle and 0.1 mg/kg treatment. Oral activity was enhanced following drug administration (Fig 5). Both the 1.0 and 0.3 mg/kg doses elevated oral activity compared with the lower doses. The 1.0 mg/kg dose did this for the entire time course while 0.3 mg/kg elevated oral activity for the initial 45 min. None of the other behaviors were significantly altered by apomorphine treatment.

When HR and LR were compared, LR had lower behavioral scores compared with HR for two highest doses tested (Fig. 1C). For the individual components of behavior there were differences between HR and LR in locomotor activity, rearing, and oral activity. Locomotor activity was enhanced in HR compared with LR following all doses (Fig. 3). This was over nearly the entire timecourse for the 0.3 mg/kg dose. Rearing was significantly increased in HR compared with LR following the 0.3 mg/kg dose. Oral activity was also greater in HR compared with LR following both the 0.3 and 1.0 mg/kg doses. This was in the initial 35 min after 0.3 mg/kg and over a majority of the timecourse following the 1.0 mg/kg dose. There were no differences between HR and LR rats for the other observed behaviors. Vehicle treatment did not produce any differences between HR and LR in any of the activities monitored (data not shown).

Response to the selective D_1 agonist SKF 38393

SKF 38393 produced behavioral activation at all doses tested (Fig. 1D). However, this activation was not dose dependent. All doses of SKF-38393 increased the behavioral rating score compared with vehicle treatment. For the individual components of behavior there were also treatment effects. Sniffing (Fig. 2) was significantly increased at all doses tested, with both the 10 and 40 mg/kg doses producing more sniffing than the 2.5-mg/kg or ve-

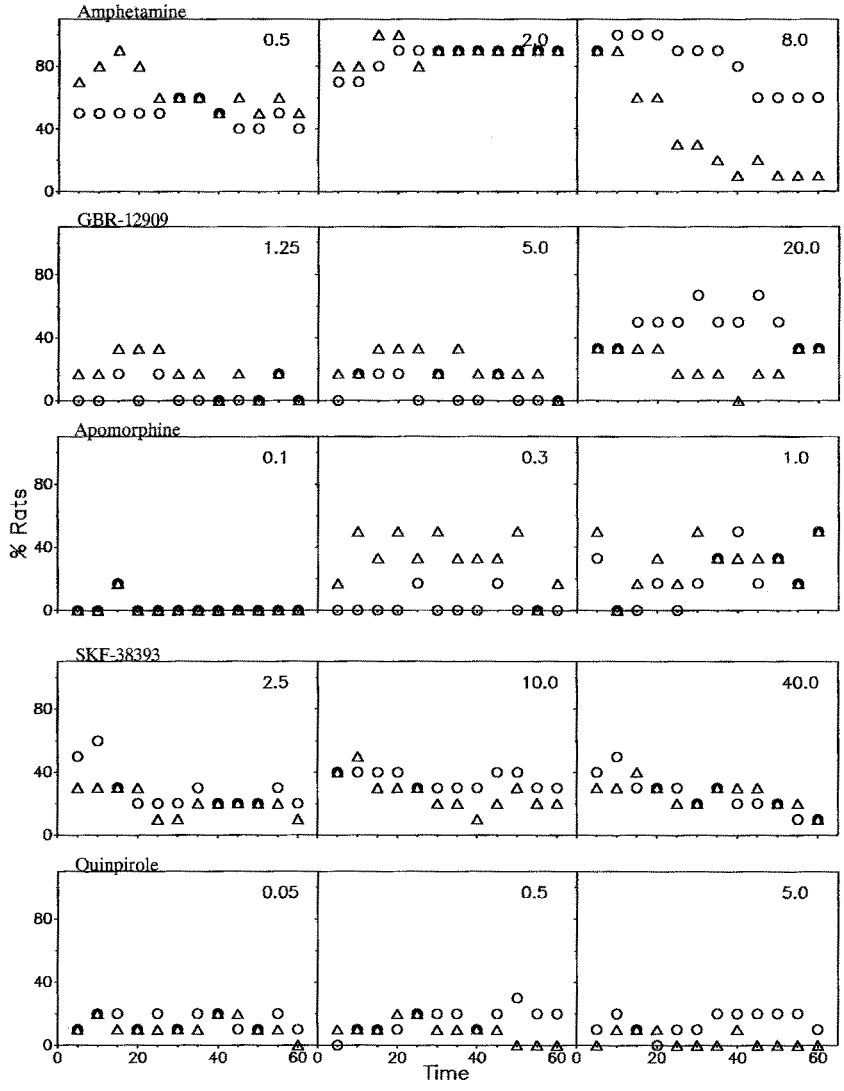

Fig. 4. Percentage of rats displaying rearing following amphetamine, GBR-12909, apomorphine, SKF-38393, or quinpirole. The dose of drug expressed in mg/kg is in the *upper right corner* of each graph. ○, LR; △, HR

hicle doses. Locomotor activity (Fig. 3) was not significantly increased by SKF 38393 administration. Subjects displayed increased rearing (Fig. 4) following all doses of SKF 38393 compared with vehicle treatment. Likewise, all doses of SKF 38393 tested produced increases in grooming (data not shown) and intense grooming (data not shown) compared with vehicle. However, increase in these behaviors were not dose dependent. There were no effects of SKF 38393 administration on oral activity (Fig. 5).

There was a trend for HR to have a greater behavioral score (Fig. 1) than LR for all doses tested ($P < 0.10$). No difference between HR and LR was observed in any of the individual behaviors monitored.

Behavioral response to the selective D_2/D_3 agonist quinpirole

Quinpirole produced a dose-dependent behavioral activation at the two highest doses tested (Fig. 1E). This is evident in the behavioral rating as the two highest doses of quinpirole produced an increased behavioral rating score compared with vehicle and the 0.5 mg/kg treatment. For the individual components of behavior there were dose-dependent effects of quinpirole on sniffing, locomotor activity, and oral activity. Sniffing (Fig. 2) was significantly increased following all doses tested. The 5 and 0.5 mg/kg doses elevated sniffing compared with the other two treatments. Locomotor activity (Fig. 3) and oral activity (Fig. 5) were also increased by the two highest doses of quinpirole tested. Quinpirole did not significantly alter the other behaviors. Differences between HR and LR in the behavioral rating or for any of the specific behaviors monitored were not observed in response to quinpirole.

Discussion

Previous studies have shown that HR have a greater locomotor response to amphetamine than LR (Piazza et al. 1989; Hooks et al. 1991a), and have fewer dopamine D_2 receptor binding sites and less D_2 mRNA in the nucleus accumbens and striatum (Hooks et al. 1993). In the current experiment, HR exhibited an increased behavioral

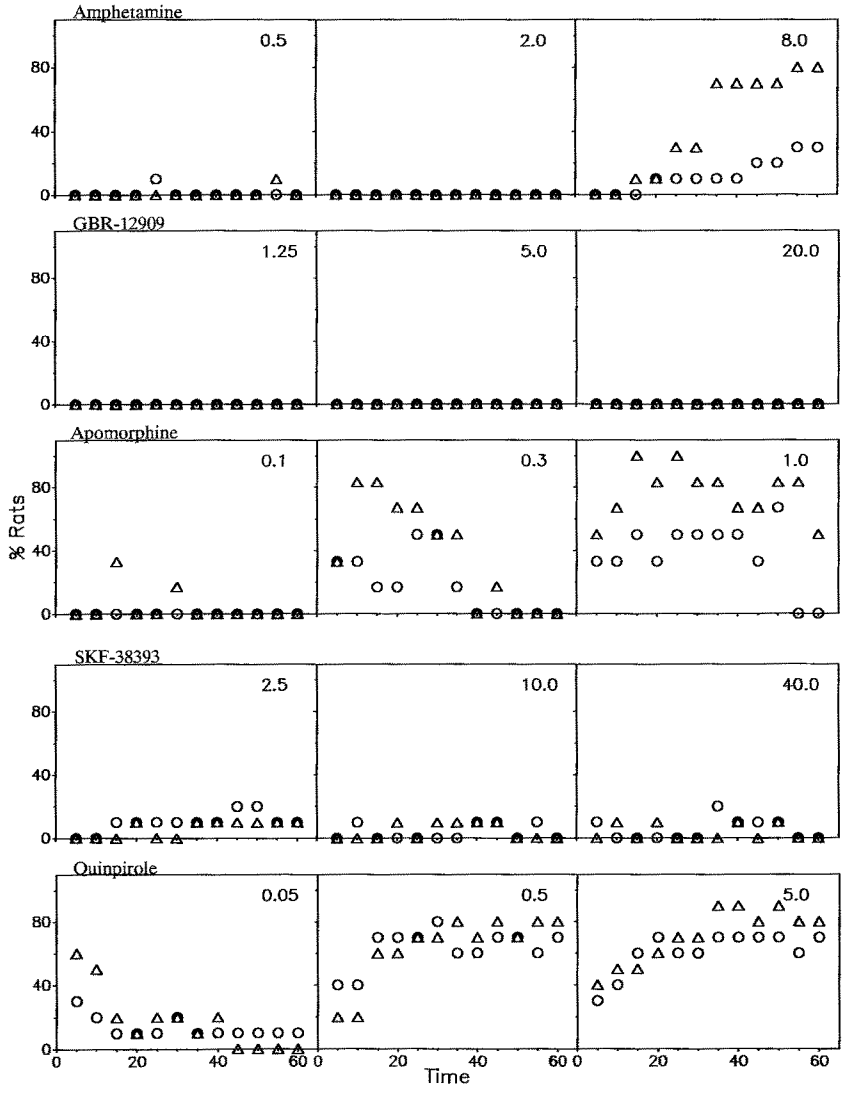

Fig. 5. Percentage of rats displaying oral activity following amphetamine, GBR-12909, apomorphine, SKF-38393, or quinpirole. The dose of drug expressed in mg/kg is in the *upper right corner* of each graph. ○, LR; △, HR

response to amphetamine, GBR-12909, and apomorphine administration compared with LR. There were no significant differences between HR and LR in their behavioral response to administration of the selective D_1 agonist SKF-38393 or the selective D_2/D_3 agonist quinpirole. These results indicate that while there may be differences in the number of specific dopamine receptors, selective activation of a single dopamine receptor subtype is not sufficient to reveal significant behavioral differences between HR and LR using the current methods. This may be due to the greater amount of locomotor activity and stereotypic behavior (focused sniffing, licking and biting) produced by amphetamine, GBR-12909, and apomorphine compared with the selective agonist.

In the current and past experiments (Piazza et al. 1989; Hooks et al. 1991a, 1992a,c) amphetamine administered systemically produced a greater behavioral response in HR than LR. HR showed greater behavioral activation at all doses of amphetamine tested compared with LR. Compared with LR, HR have a greater level of gross behaviors, such as rearing and locomotor activity (Hooks et al. 1991a), following administration of low doses of amphetamine. Following higher doses of amphetamine, HR exhibit more intense stereotypic behaviors, such as licking and biting, compared with LR. From these data it appears that amphetamine produces an overall greater behavioral activation in HR compared with LR, shifting the dose-response curve to the left for several components of the behaviors observed following amphetamine. This may explain why a previous experiment (Hooks et al. 1992a) did not show differences between HR and LR in locomotor activity following an intermediate dose of amphetamine (1.5 mg/kg). Competing behaviors were probably occurring in HR, obscuring the differences between the groups.

The results of recent studies have suggested that the differences between HR and LR in their level of behavioral activation may be due to differences in the dopaminergic system (Bradberry et al. 1991; Hooks et al. 1992b). HR show a greater increase in extracellular dopamine following administration of either cocaine or amphetamine compared with LR (Bradberry et al. 1991; Hooks et al. 1991b, 1992c). In addition, HR and LR differ in dopamine turnover following exposure to a novel environment (Piazza et al. 1991). The results with GBR-12909 further support the role of dopamine in individual differ-

ences. GBR-12909, which is a specific dopamine uptake blocker (Heikkila and Manzino 1984), revealed profound differences between HR and LR in sniffing, locomotor activity, and rearing. While amphetamine, GBR-12909, apomorphine, and quinpirole all produced increases in locomotor activity, the intensity of the locomotor activity produced by GBR-12909, amphetamine, and apomorphine was much greater than that produced by quinpirole. GBR-12909, amphetamine, and apomorphine, in addition to producing a high degree of locomotor activity, can also produce more focused stereotypies (i.e., focused sniffing, licking and biting). High doses of amphetamine administered acutely in the present and in past experiments (Segal 1975) produced focused stereotypic behavior. Chronic treatment with a high dose of GBR-12909 (20 mg/kg) has also been shown to produce focused stereotypic behaviors (Kelley and Lang 1989). It may require activation of multiple dopamine receptor types to produce high levels of locomotor activity and intense stereotypic behaviors. As indicated by the apomorphine, amphetamine, and GBR-12909 data, activation of a combination of dopamine receptor types may also be necessary to produce individual differences as predicted by locomotor response to novelty.

The present results support this hypothesis, as administration of either dopamine D_1 or D_2/D_3 agonists produced increases in certain behaviors while producing no differences between HR and LR. The D_1 agonist SKF 38393 caused large increases in the amount of sniffing, grooming, and intense grooming observed in subjects, while the D_2/D_3 agonist quinpirole increased sniffing, locomotor activity, and oral activity in subjects. These results were similar to the effects observed previously following administration of D_1 and D_2/D_3 agonists (Sharp et al. 1990; Ujike et al. 1990). These experiments also showed that SKF 38393 caused increases in the amount of sniffing, grooming, and intense grooming while not greatly changing locomotor activity and rearing, while quinpirole increased sniffing and locomotor activity and had no effect on grooming. While both D_1 and D_2/D_3 agonists produced behavioral activation, neither produced differences in overall behavioral activation between HR and LR. This is in contrast to previous work that showed that prior exposure to electroconvulsive shock increased the behavioral response to administration of selective D_1 agonists but not D_2/D_3 agonists (Sharp et al. 1990), while prior repeated exposure to methamphetamine or cocaine increased the behavioral response to selective D_2/D_3 agonists but not D_1 agonists (Ujike et al. 1990). This would suggest that the underlying differences between HR and LR are not identical to those between drug- or environment-sensitized and naive subjects. However, it is important to note that the behavioral profiles elicited by administration of either D_1 or D_2/D_3 agonists do not match the behavioral profile of subjects following amphetamine, apomorphine or GBR-12909 administration as previously stated.

The fact that the behavioral profiles of subjects following selective dopamine agonists are different from those following amphetamine, apomorphine or GBR-12909 leads to several possible reasons why HR and LR do not differ in their behavioral response to selective dopamine agonists. One is that the visual scoring of subjects is not sufficiently sensitive to detect differences between HR and LR. This does not seem to be the case, since visually scoring subjects allowed the determination of differences between HR and LR in response to amphetamine and GBR-12909 in the current experiment and between subjects exposed to ECS or chronic amphetamine or cocaine in previous experiments (Sharp et al. 1990; Ujike et al. 1990). Another explanation for the lack of differences between HR and LR following D_1 and D_2/D_3 agonists is that there are not only differences in the number of receptors between HR and LR, but also in the second messenger systems of receptors. There is recent evidence to support this hypothesis. HR and LR differ in cAMP dependent protein kinase and tyrosine hydroxylase levels (Miserendino et al. 1992). It is possible that administration of direct agonists causes the difference in number of receptors and level of second messengers to cancel each other and level of behavioral activation to be equal between the groups.

The current results strongly support the hypothesis that activation of a combination of dopamine receptor types are needed to produce behavioral differences in activation between HR and LR. Indirect activation of dopamine receptors by increasing extracellular dopamine following amphetamine and GBR-12909 administration produces differences between HR and LR. It is possible that this finding is observed because administration of indirect agonists and exposure to the novel environment increase rapid locomotor activity. In addition, administration of a nonselective agonist, which also produces more robust locomotor activity, produced differences between HR and LR rats. Response to novelty does not predict the behavioral response to selective and direct acting D_1 or D_2/D_3 agonists. The reason for this may be that the selective direct agonists do not increase locomotor activity and focused stereotypic behaviors to a large extent. It seems likely that the increased behavioral activation by the indirect agonists and nonspecific agonist are caused by the activation of all receptor subtypes simultaneously. This appears to be necessary to produce individual differences based on locomotor response to a novel environment.

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