Pharmacology Biochemistry and Behavior, Vol. 66, No. 1, pp. 113–121, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(00)00206-9

An Assessment of Novelty-Seeking Behavior in Alcohol-Preferring and Nonpreferring Rats

K. L. NOWAK,* C. M. INGRAHAM,* D. L. MCKINZIE,*[1] W. J. MCBRIDE,* L. LUMENG,† T.-K. LI† AND J. M. MURPHY*‡

*Departments of *Psychiatry and*
†Medicine, Institute of Psychiatric Research, Indiana University School of Medicine IUPUI & †VAMC, and
‡Department of Psychology, Purdue School of Science, Indianapolis, IN

Received 18 October 1999; Revised 24 January 2000; Accepted 24 January 2000

NOWAK, K. L., C. M. INGRAHAM, D. L. MCKINZIE, W. J. MCBRIDE, L. LUMENG, T.-K. LI AND J. M. MURPHY. *An assessment of novelty-seeking behavior in alcohol-preferring and nonpreferring rats*. PHARMACOL BIOCHEM BEHAV **66**(1) 113–121, 2000.—This study examined novelty-seeking behavior in rat populations selectively bred for high and low alcohol-drinking behavior. In Experiment 1, and "odor-enhanced" novel environment produced greater behavioral activation in P compared to NP rats. In Experiment 2, the activity of high alcohol-drinking P and HAD rats was enhanced to a greater extent following the presentation of novel odors in a familiar arena, compared to the NP and LAD rats. The results suggest that, when measuring locomotor activity, alcohol-preferring rats are more reactive to novelty than their nonpreferring counterparts. Experiments 3 and 4, however, did not support the hypothesis that novelty seeking is associated with genetic vulnerability to high alcohol-drinking behavior. When measuring nose-poking behavior in response to novel odors and preference for a novel vs. a familiar chamber, behavior of the preferring lines did not differ from that of the nonpreferring lines, although P rats were more active in the place-preference paradigm. The overall results indicate that the relationship between novelty and alcohol drinking is only modestly associated, and is observed under specific conditions. Moreover, this study underscores the importance of using multiple measures when assessing complex behaviors such as novelty seeking. © 2000 Elsevier Science Inc.

Novelty seeking Alcohol-preferring rats Alcohol nonpreferring rats Locomotor activity Type II alcoholism

CONSIDERABLE research indicates that alcohol preference and alcohol abuse contain a strong genetic component (10,28,30). Type II alcoholism, in particular, is highly heritable, and distinguished primarily by the individuals early alcohol-drinking behavior and family history of alcoholism (11). Type II alcoholism is also identified by a triad of personality traits: high novelty seeking, low reward dependence, and low harm avoidance (7,11,27,49).

The personality trait of high novelty seeking, like Type II alcohol abuse, is believed to have strong heritability (15,22,36,37). Novelty seeking refers to behavioral activation in the presence of unknown stimuli (11). Its purpose is to increase exploratory activity along with locomotor activity, which is necessary to promote survival functions such as the search for food, a sexual mate, shelter, and to relieve boredom (2). Clinical studies indicate that high novelty-seeking behavior is highly predictive of current and future alcohol abuse (1,4,21,44,45,50).

Numerous studies have confirmed the importance of the mesolimbic dopamine system in the reinforcing properties of drugs of abuse (5,8,18,26,38,43,46). It has been suggested that a common neural circuitry underlies drug reward and novelty-seeking behavior (2,3,6,20,25,34,40). Exposure to novelty activates some of the same neural substrates that mediate the rewarding effects of drugs of abuse (2,25,42). In addition, rats identified as high responders to novelty show increased alcohol and drug intake in comparison to low responders, and show abnormalities within the mesolimbic region of the brain (17,23).

As yet, little is known of whether genetic-based animal models of alcoholism express phenotypic traits associated

[1]Current address: Lilly Research Laboratories, Eli Lilly & Co., DCOS10, Indianapolis, IN 46285.
Requests for reprints should be addressed to James M. Murphy, Department of Psychology, Purdue School of Science, 402 N. Blackford St., IUPUI, Indianapolis, IN 46202-3275.

with the clinical profile of Type II alcoholism. The objective of this study was to determine whether differences in novelty-seeking behavior exist in rat populations selectively bred for high and low alcohol-drinking behavior. It was hypothesized that rats selectively bred for high alcohol-drinking behavior would exhibit high novelty-seeking behavior.

EXPERIMENT 1: LOCOMOTOR ACTIVITY IN A "PLAIN" OR "ODOR-ENHANCED" CONTEXT

This study examined locomotor activity in an open field arena in adult P and NP ethanol-naive rats. Male P and NP rats ($n = 10$ per line) from the 41st generation were double housed in plastic tubs (23 × 43 × 20 cm W × L × H) and maintained on a standard light/dark cycle (lights on at 0900 h) with ad lib food and water. The experimental protocols used were approved by the Institutional Animal Care and Use Committee, and all procedures are in compliance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (Publication #85-23; 1985). Animals were approximately 120–150 days of age at the beginning of the experiment and weighed approximately 450 ± 35 g. Rats were placed in either a "plain" or "odor-enhanced" context (order counterbalanced) for a 60-min activity assessment. One week later, rats were exposed to the alternate context, and locomotor activity was recorded for 60 min. The "plain" context consisted of clean pine shavings on the floor of a clear Plexiglas chamber (40.5 × 40.5 × 30.5 cm W × L × H). The "odor-enhanced" context utilized a similar chamber but contained, in each corner, a different odor (orange, maple, peppermint, and banana) placed beneath a wire mesh floor. Cumulative activity was recorded in 5-min blocks with the use of multiple photocell beams (Opto-Varimex-Minor, Columbus Instruments, Columbus, OH); each beam crossing was designated as one activity count.

Results

Figure 1 illustrates open field activity in P (top) and NP (bottom) rats in the "plain" and "odor-enhanced" contexts. Data are mean activity counts in 5-min intervals for the first 30 min of the 60-min session, because the majority of activity occurred within this time frame. A mixed ANOVA (line × context × time) revealed significant main effects of context, $F(1, 18) = 40.35$ $p < 0.0001$, and time, $F(5, 90) = 58.48$, $p < 0.0001$, but not of line, $F(1, 18) = 2.89$, $p > 0.05$. There were, however, significant line × context, $F(1, 18) = 4.37$, $p < 0.05$, line × time, $F(5, 90) = 3.98$, $p < 0.01$, and context × time, $F(5, 90) = 13.9$, $p < 0.0001$, interactions. The analysis also revealed a significant three-way interaction, $F(5, 90) = 2.61$, $p < 0.05$. Student's *t*-tests revealed that, within the first 5 min of being placed in the "odor-enhanced" context and the first 10 min of being placed in the "plain" context, activity of the P rats was significantly higher ($p < 0.05$) than that of the NP rats. Additionally, activity of the P rats increased by over 100% during the first 5 min of being placed in the "odor-enhanced" context (510 ± 75 vs. 1050 ± 176 activity counts) compared to a 71% increase in NP rats (353 ± 45 vs. 602 ± 97 activity counts). Moreover, the increased activity of the P rats in the enhanced context persisted longer than the activity of the NP rats ($p < 0.05$).

EXPERIMENT 2: LOCOMOTOR ACTIVITY FOLLOWING THE PRESENTATION OF NOVEL ODORS

Experiment 2 assessed locomotor activity in response to novel odors following habituation to the test arena. Adult

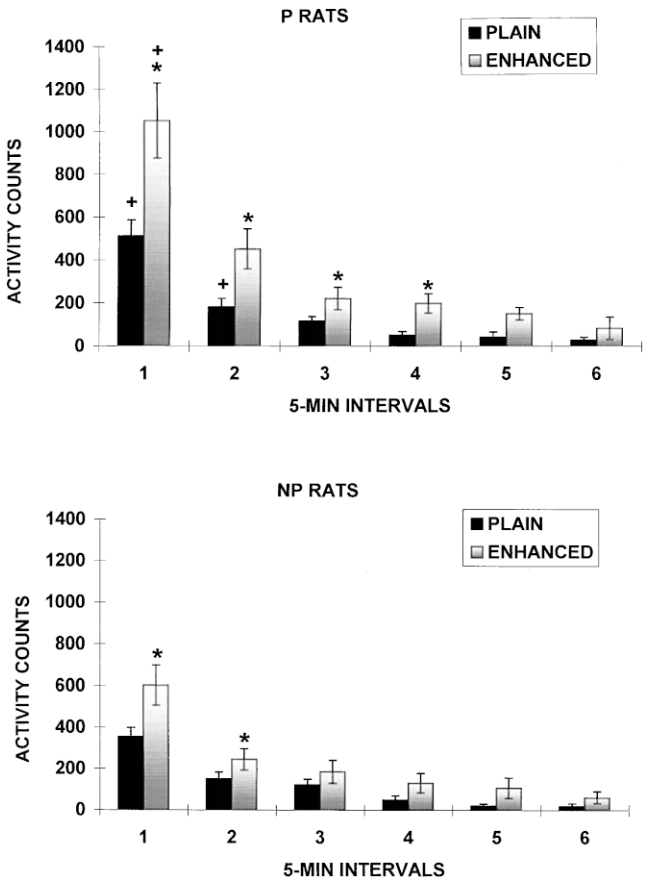

FIG. 1. Locomotor activity in a "plain" vs. "odor-enhanced" context in P (top panel) and NP (bottom panel) rats. Data are mean activity counts for the first 30 min of the 60-min session. $^{*}p < 0.05$, "plain" vs. "enhanced" context; $^{+}p < 0.05$, P vs. NP rats.

ethanol-naive male P and NP ($n = 12$ per line) and HAD-I and LAD-I ($n = 21$ and 24 per line, respectively) rats from the 42nd and 28th generations were tested. Animals were approximately 120–150 days of age, and weighed approximately 450 ± 50 and 350 ± 50 g, respectively, at the beginning of the experiment. Housing conditions were as described in Experiment 1. For 3 days, rats were placed in the clear Plexiglas chamber (40.5 × 40.5 × 30.5 cm W × L × H) with clean pine shavings on the floor for a 30-min habituation period. On day 4, animals received 15 min of habituation to the chamber and were then presented with two cotton balls with 0.25 ml each of banana and orange extract, placed at opposite ends of the chamber. Activity was recorded for an additional 30 min. Cumulative activity for habituation and test session was recorded with the use of multiple photocell beams; each beam crossing was designated as one activity count.

Results

Figure 2 illustrates activity counts for the three 30-min habituation sessions in P and NP (left), and HAD and LAD rats (right). Data analysis consisted of separate two-way repeated-measures ANOVAs (line × day) on total activity for the P vs. NP rats and the HAD vs. LAD rats. There were

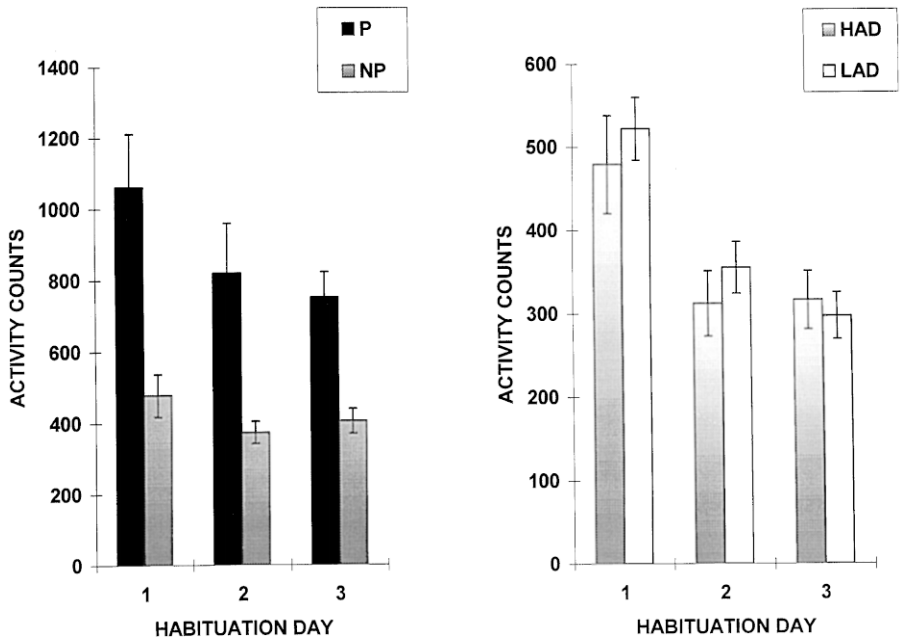

FIG. 2. Total activity counts for the three 30-min habituation sessions to the activity chamber in P and NP (left panel), and HAD and LAD rats (right panel).

significant effects of both line, $F(1, 22) = 16.4$, $p < 0.001$, and day, $F(2, 44) = 6.4$, $p < 0.01$, but not a significant line × day interaction, $F(2, 44) = 2.0$, $p > 0.05$, for the P and NP rats. P rats decreased their activity from a mean of 1061 ± 149 activity counts on day 1 to 819 ± 140 and 751 ± 71 on days 2 and 3, whereas activity of the NP rats did not change over the 3 days (477 ± 60, 372 ± 31, and 404 ± 35 counts, respectively). Analysis of baseline activity for the HAD and LAD rats did not reveal a significant main effect of line, $F(1, 22) = 0.49$, $p > 0.05$, nor a significant line × day interaction, $F(2, 44) = 0.86$, $p > 0.05$. There was, however, a significant effect of day, $F(2, 44) = 29.03$, $p < 0.0001$. Thus, activity of both the P/NP and the HAD/LAD lines habituated over the three sessions. Moreover, P rats exhibited consistently higher activity levels over the three habituation days than did NP rats.

Figure 3 represents mean activity counts in 5-min intervals for the 15-min habituation period prior to, and the 30 min following the presentation of odors in P and NP (left), and HAD and LAD rats (right) on the test day. Analysis of activity during the 15-min habituation period by two-way repeated-measures ANOVAs (line × time) in P and NP rats revealed a significant main effect of time, $F(2, 44) = 54.5$, $p < 0.0001$, but not of line, $F(1, 44) = 3.3$, $p > 0.05$. In addition, there was not a significant time × line interaction, $F(2, 44) = 2.5$, $p > 0.05$. Similarly, there was a significant main effect of time, $F(2, 88) = 61.61$, $p < 0.0001$, but not of line, $F(1, 44) = 0.39$, $p > 0.05$, for the HAD and LAD rats. There was not a significant time × line interaction, $F(2, 88) = 0.69$, $p > 0.05$. Thus, all rats habituated to the environment during the first 15 min, and mean activity counts did not differ between P and NP rats nor between HAD and LAD rats prior to the presentation of the odors.

Analysis of 30-min activity following the presentation of odors for P and NP rats using a Student's *t*-test revealed that P rats increased activity in response to the novel odors significantly more than NP rats [385 ± 44 vs. 264 ± 30 activity counts, $t(22) = 2.3$, $p < 0.05$]. Furthermore, HAD rats increased activity in response to the novel odors significantly more than LAD rats [71 ± 15 vs. 37 ± 9 activity counts, $t(43) = 2.1$, $p < 0.05$].

EXPERIMENT 3: NOSE-POKING BEHAVIOR AS AN ASSESSMENT OF NOVELTY SEEKING

This experiment examined nose-poking behavior of rats habituated to the test arena following the presentation of novel odors as an assessment of novelty-seeking behavior. Male P and NP ($n = 10$ per line) and HAD-I and LAD-I ($n = 8$ per line) ethanol-naive rats from the 42nd and 28th generations were used for this experiment. Animals were approximately 120–150 days of age and weighed approximately 450 ± 50 and 350 ± 50 g, respectively, at the beginning of the experiment. Housing conditions were as described in Experiment 1. For four consecutive days, animals were habituated to the testing chamber by receiving 15 min of exposure to a dark rectangular chamber (45 × 25 × 37.5 cm L × W × H) with two equispaced 1-cm holes drilled into each side. On test day, animals received a single 15-min exposure to the chamber with the addition of banana extract (0.25 ml) presented behind each hole. Animals were videotaped and tapes were scored by a blind observer with the aid of a computer scoring program that recorded total number of nose pokes in the session (frequency) and the total time spent nose poking (duration).

Results

The frequency and duration of nose-poking behavior in P and NP rats and HAD and LAD rats for the first and fourth habituation days are illustrated in Fig. 4. Total nose-

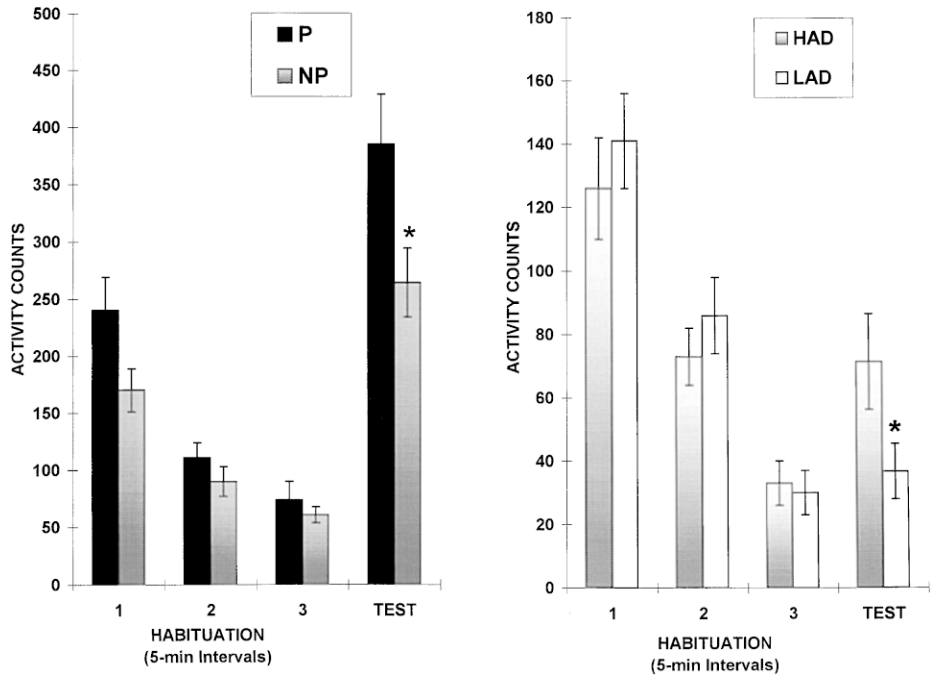

FIG. 3. Locomotor activity following the presentation of novel odors in P and NP (left panel) and HAD and LAD (right panel) rats. Data are mean activity counts for the 15-min habituation session prior to testing and the 30-min test following the presentation of odors. $*p < 0.05$, preferring vs. nonpreferring rats.

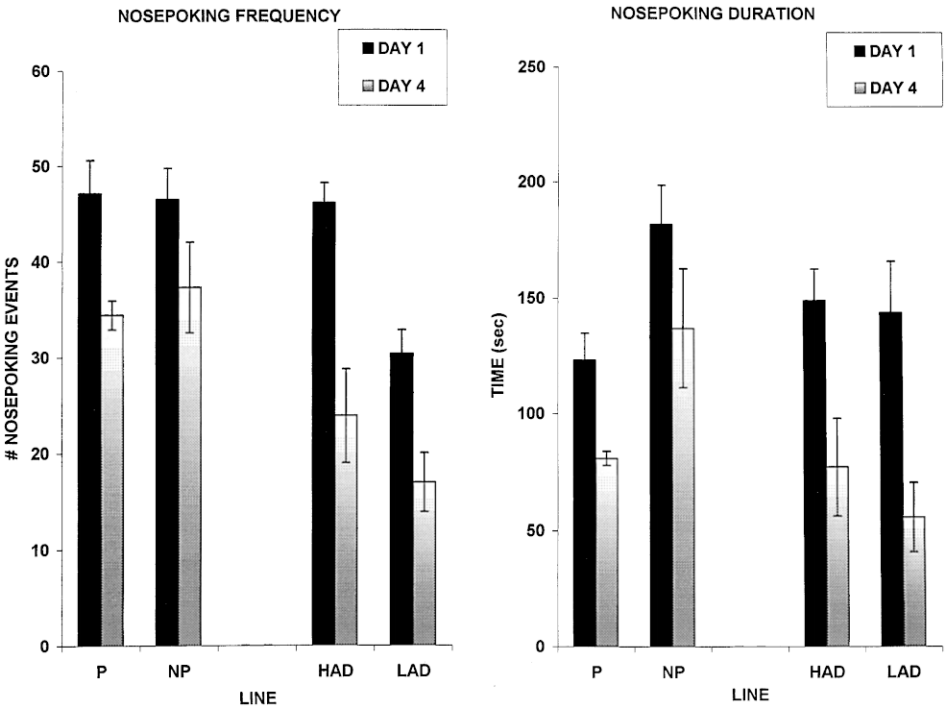

FIG. 4. Total nose-poking frequency (left panel) and duration (right panel) during the first and fourth days of habituation to the chamber in preferring (P and HAD) and nonpreferring (NP and LAD) rats.

poking frequency and duration for the first and fourth days of habituation were analyzed using separate two-way repeated-measures ANOVAs (line × test) for P vs. NP and HAD vs. LAD rats. The frequency analysis for the P and NP lines (Fig. 4, left) revealed a significant effect of test, $F(1, 18) = 12.17$, $p < 0.01$. There was not a significant effect of line, $F(1, 18) = 0.10$, $p > 0.05$, nor a significant line × test interaction, $F(1, 18) = 0.31$, $p > 0.05$. The frequency analysis for the HAD and LAD lines (Fig. 4, left) revealed a significant effect of test, $F(1, 14) = 60.69$, $p < 0.0001$. There was not a significant effect of line, $F(1, 14) = 3.34$, $p > 0.05$, nor a significant line × test interaction, $F(1, 14) = 0.0005$, $p > 0.05$.

The duration analysis for the P and NP lines (Fig. 4, right) revealed significant effects of line, $F(1, 18) = 10.68$, $p < 0.005$, and test, $F(1, 18) = 8.08$, $p < 0.01$. There was not a significant line × test interaction, $F(1, 18) = 0.01$, $p > 0.05$. The duration analysis for the HAD and LAD lines (Fig. 4, right) revealed a significant effect of test, $F(1, 14) = 48.37$, $p < 0.0001$. There was not a significant effect of line, $F(1, 14) = 0.34$, $p > 0.05$, nor a significant line × test interaction, $F(1, 14) = 0.49$, $p > 0.05$. Therefore, all rats habituated to the testing chamber in a similar manner. The duration of nose-poking behavior for NP rats, however, was longer than P rats for both habituation tests.

Analyses of nose-poking frequency and duration during the presentation of novel odors was done on 5-min intervals using separate two-way repeated-measures ANOVAs (time × line) for the P vs. NP and HAD vs. LAD rats (Figs. 5 and 6). The analysis of nose-poking frequency for P and NP rats (Fig. 5, left) revealed that there was a significant effect of time, $F(2, 36) = 12.6$, $p < 0.0001$. There was not a significant effect of line, $F(1, 18) = 0.02$, $p > 0.05$, nor a significant time × line interaction, $F(2, 36) = 0.91$, $p > 0.05$. Similarly, there was a significant effect of time, $F(2, 28) = 21.97$, $p < 0.0001$, for the HAD and LAD rats (Fig. 5, right). There was not a significant effect of line, $F(1, 14) = 2.72$, $p > 0.05$, nor a significant time × line interaction, $F(2, 28) = 1.08$, $p > 0.05$. Nose-poking frequency was greatest for all rats during the first 5 min of the 15-min test and no line differences were observed.

The analysis of nose-poking duration for P and NP rats (Fig. 6, left) revealed that there was a significant effect of time, $F(2, 36) = 11.02$, $p < 0.001$. The effect of line $F(1, 18) = 1.25$, $p > 0.05$, and the time × line interaction, $F(2, 36) = 0.91$, $p > 0.05$, were not significant. The effect of time, $F(2, 28) = 11.02$, $p < 0.001$, on duration of nose-poking behavior for the HAD and LAD rats (Fig. 6, right) was also significant. There was not a significant effect of line, $F(1, 14) = 1.25$, $p > 0.05$, nor a significant time × line interaction, $F(2, 28) = 0.93$, $p > 0.05$. Nose-poking duration was longer for all rats during the first 5 min of the 15-min test.

EXPERIMENT 4: NOVELTY ASSESSMENT USING PLACE PREFERENCE

Experiment 4 examined preference for a familiar vs. a novel environment in male P and NP rats ($n = 9$ per line). Animals from the 42nd generation were approximately 120–150 days of age at the beginning of the experiment and weighed 485 ± 70 g. The animals were given 4 days of 30-min exposure to one of two sides of a rectangular chamber (sides counterbalanced). Half of the chamber had a black floor with white sides and the other a white floor with black sides. Each side measured 38.5 × 38.5 × 38.5 cm (L × W × H) and was divided by a 9.5 × 38.5 × 38.5 cm gray "crossing zone" with a 9.5 × 5 × 5 cm opening. On the fourth day,

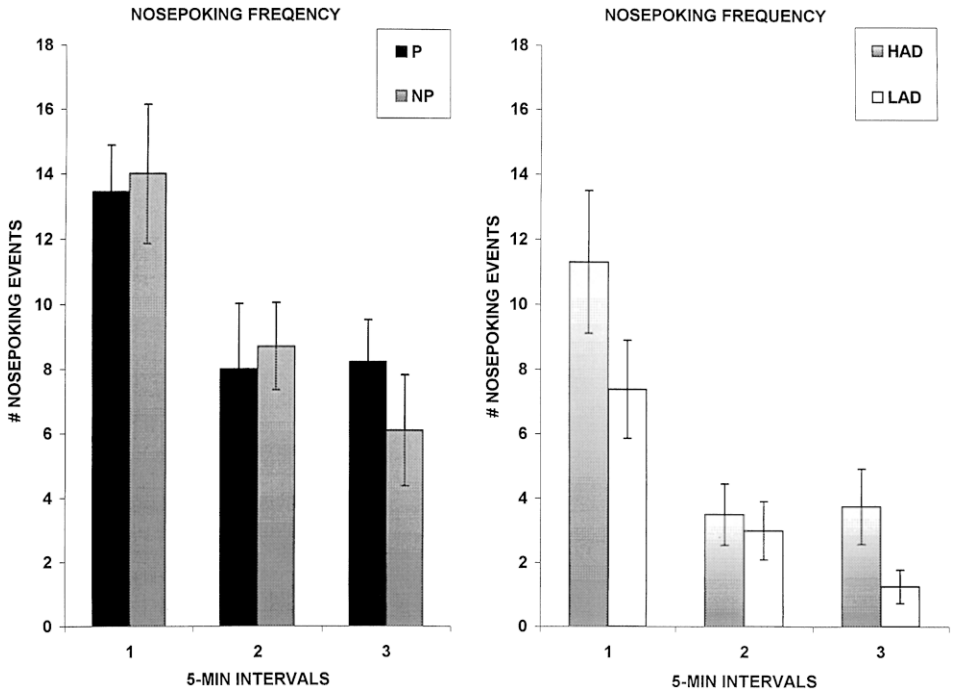

FIG. 5. Nose-poking frequency during the 15-min test session in P and NP (left panel) and HAD and LAD (right panel) rats.

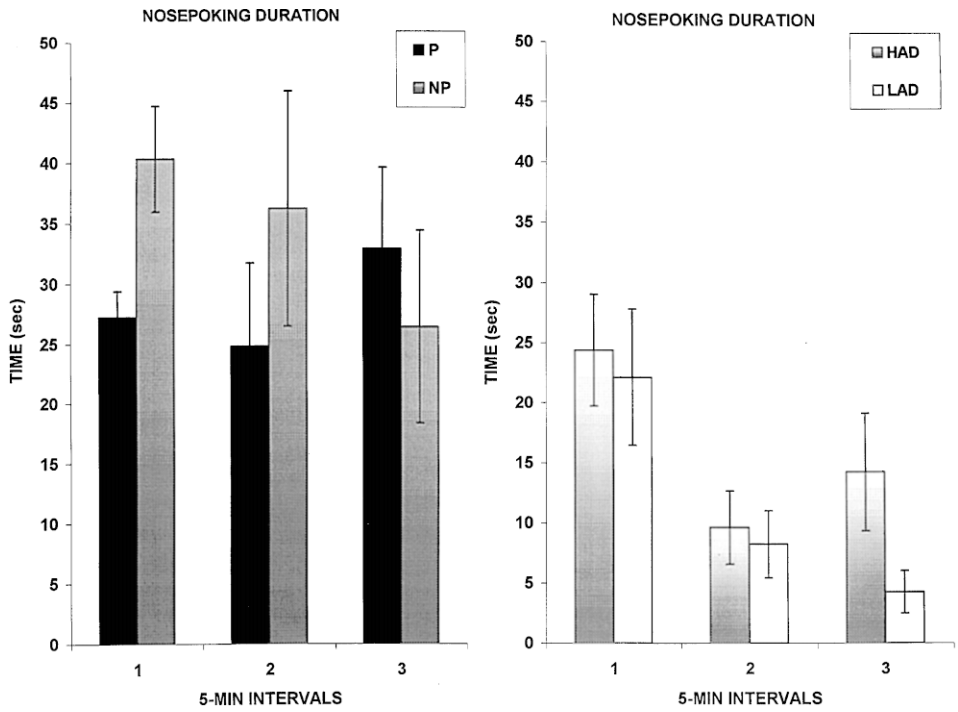

FIG. 6. Duration of nose-poking behavior during the 15-min test session in P and NP (left panel) and HAD and LAD (right panel) rats.

rats were given a 15-min preference test. Animals were initially placed in the familiar side. When the rat's head and at least the two front limbs entered the novel side, it was deemed a crossing. Animals were videotaped and tapes were scored by a blind observer with the aid of a computer scoring program that recorded duration of time spent on each side, latency to initial crossing to the novel side, and number of crossings.

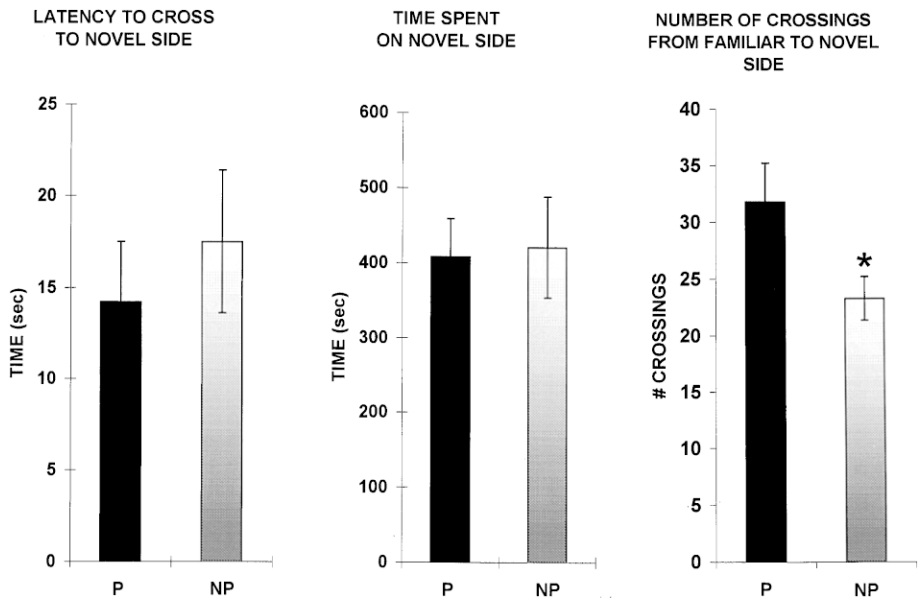

FIG. 7. Mean latency to cross to the novel side (left panel), time spent on the novel side (middle panel), and number of crossings from familiar to novel side in P and NP rats in a place preference paradigm. $*p < 0.05$, preferring vs. nonpreferring rats.

Results

Figure 7 illustrates latency to cross to the novel side (left), time spent on the novel side (middle) and the number of crossings to the novel side of the chamber (right) in P and NP rats. Student's *t*-tests used to analyze duration and latency to cross did not reveal differences between P and NP rats on either measure, $t(15) = 0.16$, $p > 0.05$, and $t(15) = 0.644$, $p > 0.05$, respectively. The analysis of number of crossings to the novel side, however, did reveal a significant line effect (32 ± 3.4 vs. 23 ± 2 activity counts; $t(15) = 2.10$, $p = 0.05$. The P rats crossed significantly more to the novel side than did the NP rats. One NP animal never crossed to the novel side and was thus excluded from the analyses.

GENERAL DISCUSSION

The primary finding of the present research suggests that, when measuring locomotor activity in response to novel stimuli, consistent line differences are seen between alcohol-preferring and nonpreferring rats. Experiment 1 found that the "odor-enhanced" environment produced greater and longer behavioral a activation in the locomotor orienting response in P compared to NP rats. The results of Experiment 2 demonstrate that locomotor activity in high alcohol-drinking P and HAD rats is enhanced to a greater extent in a familiar environment following the presentation of novel odors than in their low alcohol-drinking counterparts. Additionally, the number of crossings to the novel side in a place preference paradigm was significantly greater for P compared to NP rats. The above results suggest that there is higher novelty-seeking behavior in preferring, vs. nonpreferring lines.

Experiments 3 and 4, however, do not support the hypothesis that high novelty-seeking behavior is associated with genetic vulnerability to high alcohol-drinking behavior. When measuring nose-poking behavior in response to novel odors and preference for a novel vs. a familiar area, behavior of the preferring lines did not differ from that of the nonpreferring lines.

One possible reason for the differences between the first two and the second two experiments may be the use of locomotor activity, vs. nose-poking or place preference behavior, as a dependent measure. Piazza et al. (39) and Hooks et al. (24) determined that rats demonstrating high locomotor activity in response to a novel environment (High Responding or HR rats) show increased locomotor activity in response to an amphetamine challenge compared to their low-responding (LR) counterparts. An animal's response to place preference for novelty or exposure to a novel object, however, was not predictive of its locomotor response to amphetamine (42). Exner and Clark (19) examined the behavior of nonclassified animals to an inescapable, novel environment and categorized the animals' responses as "escape" and "exploratory" behaviors. After exposure to an inescapable novel environment, "escape" behavior (defined as rearing, sniffing upward, increased activity) was shown to correlate with the locomotor stimulant effect of amphetamine, but the "exploration" factor (sniffing downward, immobile) was not. "Escape" behaviors are thus thought to represent the stressful component of novelty, and indeed, exposure to novelty results in increased corticosterone levels (16). Conversely, "exploratory" behavior is thought to represent the rewarding aspects of novelty and is elicited in familiar, "stress-free" environments, and does not result in increased levels of corticosterone (33). The distinction between locomotor activity ("escape" behavior) and "exploratory" behavior has been illuminated in a number of studies (6,12,35,41).

This classification is useful as a possible explanation as to why differences in novelty seeking were seen between alcohol-preferring and nonpreferring rats when locomotor activity was measured, vs. when nose poking or place preference was used as a dependent measure. Both nose-poking and place preference behavior can be regarded as "exploratory," because animals had free choice to visit the holes containing the odors or free choice of the different areas, in addition to the nature of the behaviors themselves (29). Experiments 1 and 2, on the other hand, can be best classified as tests examining "escape" behavior due to the measure of locomotor activity and the inescapability of the novel odors. The measure of number of crossings to the novel side in the place preference paradigm best reflects a preference of change in the P rat (17), yet also measures locomotor activity classifying it as "escape" behavior.

Previous studies have reported that alcohol-preferring rats are more "anxious" in some models of anxiety (13,31,47). As novelty seeking and anxiety are at seemingly opposite ends of the spectrum, perhaps it is more accurate to describe the P and HAD rats as being more "activated" by novelty. When novelty preference is assessed by more general measures, such as locomotor activity, P and HAD rats are more reactive than their NP and LAD counterparts. It seems plausible in the context of the above discussion that this reactivity may be nonspecific or even aversive in nature. This interpretation is further supported by a failure to observe line differences in more specific measures of exploration.

It has been suggested that a common neural circuitry underlies drug reward and novelty-seeking behavior (2,3,6,20, 25,34,40). Clinical studies indicate that high novelty-seeking behavior is highly predictive of current and future alcohol and drug abuse (1,4,21,44,45,48,50). Experiments using rats and mice have determined that there is a positive relationship between levels of novelty-seeking behavior and self-administration of drugs of abuse such as cocaine (9), amphetamine (14,32,39), nicotine (14,32), and alcohol (14,23,32). The results of the present work suggest that alcohol-preferring rats are also more reactive to novelty when measuring locomotor behavior. Thus, genetic selection for alcohol preference results in a constellation of behavioral and physiological phenotypes that are associated with heightened responsiveness to novelty.

Identifying phenotypic traits associated with high alcohol-drinking behavior may one day be a valuable behavioral marker for increased susceptibility to alcohol abuse, particularly Type II alcoholism. If such behaviors, such as a need for novelty, serve to initiate and/or maintain aberrant alcohol drinking behavior, early intervention may focus on addressing the personality profile before the alcohol abuse becomes pathological.

The overall results indicate the importance of using multiple experimental approaches in these types of behavioral studies because of the complexity of novelty-seeking behavior, and understanding the nature of various responses to novelty.

ACKNOWLEDGEMENTS

This research was supported by grants AA07611, AA07462, AA10717, and RSDA AA 00207. Special thanks to Robert S. Crile and Connie L. Dagon for their technical assistance.

REFERENCES

1. Andrucci, G. L.; Archer, R. P.; Pancoast, D. L.; Gordon, R. A.: The relationship of MMPI and sensation seeking scales to adolescent drug use. J. Pers. Assess. 53:253–266; 1989.

2. Bardo, M. T.; Donohew, R. L.; Harrington, N. G.: Psychobiology of novelty-seeking behavior. Behav. Brain Res. 77:23–43; 1996.
3. Bardo, M. T.; Neisewander, J. L.; Pierce, R. C.: Novelty-induced place preference behavior in rats: Effects of opiate and dopaminergic drugs. Pharmacol. Biochem. Behav. 32:683–689; 1989.
4. Bates, M. E.; Labouvie, E. W.; White, H. R.: The effect of sensation seeking needs on alcohol and marijuana use in adolescents. Bull. Soc. Psychol. Adict. Behav. 5:29–36; 1986.
5. Bozarth, M.; Wise, R. A.: Heroin reward is dependent on a dopaminergic substrate. Life Sci. 29:1881–1886; 1981.
6. Burns, L. H.; Annett, L.; Kelley, A. E.; Everitt, B. J.; Robbins, T. W.: Effects of lesions to amygdala, ventral subiculum, medial prefrontal cortex, and nucleus accumbens on the reaction to novelty: Implications for limbic–striatal interactions. 110:60–73; 1996.
7. Cannon, D. S.; Clark, L. A.; Leeka, J. K.; et al.: A reanalysis of the tridimensional personality questionaire (TPQ) and its relation to Cloninger's Type 2 alcoholism. Psychol. Assess. 5:62–66; 1993.
8. Carboni, E.; Imperato, A.; Perezzani, L.; Di Chiara, G.: Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. Neuroscience 28:653–661; 1989.
9. Carney, J. M.; Landrum, R. W.; Cheng, M. S.; Seale, T. W.: Establishment of chronic intravenous drug self-administration in the C57BL/6J mouse. Neuroreport 2:477–480; 1991.
10. Cloninger, C. R.: Neurogenic adaptive mechanisms in alcoholism. Science 236:410–416; 1987.
11. Cloninger, C. R.: Assessment of the impulsive-compulsive spectrum of behavior by the seven-factor model of temperament and character. In: Oldham, J. M.; Hollander, E.; Skodol, A. E., eds. Impulsivity and compulsivity. Washington, DC: American Psychiatric Press, Inc.; 1996:59–95.
12. Cole, B.; Robbins, T.; Everitt, B. J.: Lesions of the dorsal noradrenergic bundle simultaneously enhance and reduce responsiveness to novelty in a food preference test. Brain Res. Rev. 13:325–349; 1988.
13. Colombo, G.; Agabio, R.; Lobina, C.; Reali, R.; Zocchi, A.; Fadda, F.; Gessa, G. L.: Sardinian alcohol-preferring rats: A genetic animal model of anxiety. Physiol. Behav. 57:1181–1185; 1995.
14. Crabbe, J. C.; Belknap, J. K.; Buck, K. J.: Genetic animal models of alcohol and drug abuse. Science 264:1715–1723; 1994.
15. Crusio, W. E.; Schwegler, H.; van Abeelen, J. H. F.: Behavioral responses to novelty and structural variation of the hippocampusin mice. I. Quantitative-genetic analysis of behavior in the open field. Behav. Brain Res. 32:75–80; 1989.
16. Dantzer, R.; Mormede, P.: Stress in farm animals: A need for reevaluation. J. Am. Sci. 57:6–17; 1983.
17. Dellu, F.; Piazza, P. V.; Mayo, W.; LeMoal, M.; Simon, H.: Novelty-seeking in rats—Biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. Neuropsychobiology 34:136–145; 1996.
18. Di Chiara, G.; Imperato, A.: Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85:5274–5278; 1988.
19. Exner, M.; Clark D.: Behaviour in the novel environment predicts responsiveness to *d*-amphetamine in the rat: A multivariate approach. Behav. Pharmacol. 4:47–56; 1993.
20. Fink, J. S.; Smith, G. P.: Decreased locomotor and investigatory exploration after denervation of catecholamine terminal fields in the forebrain of rats. J. Comp. Physiol. Psychol. 93:34–65; 1979.
21. Forsyth, G.; Hundleby, J. D.: Personality and situation as determinants of desire to drink in young adults. Int. J. Addict. 22:653–669; 1987.
22. Fulker, D. W.; Eysenck, S. B. G.; Zuckerman, M.: A genetic and environmental analysis of sensation seeking. J. Res. Pers. 14:261–281; 1980.
23. Gingras, M. A.; Cools, A. R.: Differential ethanol intake in high and low responders to novelty. Behav. Pharmacol. 6:718–723; 1995.
24. Hooks, M. S.; Jones, G. H.; Smith, A. D.; Neill, D. B.; Justice, J. B.: Individual differences in locomotor activity and sensitization. Pharmacol. Biochem. Behav. 38:467–470; 1991.
25. Hooks, M. S.; Kalivas, P. W.: The role of the mesoaccumbens–pallidal circuitry in novelty-induced behavioral activation. Neuroscience 64:587–597; 1995.
26. Imperato, A.; Puglisi-Allegra, S.; Scrocco, M. G.; Casolini, P.; Bacchi, S.; Angelucci, L.: Cortical and limbic dopamine and acetylcholine release as neurochemical correlates of emotional arousal in both aversive and non-aversive environmental changes. Neurochem. Int. 20:265S–270S; 1992.
27. Lacy, J.; Evans, C.: The impulsivist: A multi-impulsive personality disorder. Br. J. Addict. 81:641–649; 1986.
28. Li, T.-K.; Lumeng, L.; Doolittle, D. P.: Selective breeding for alcohol preference and associated responses. Behav. Genet. 23:163–170; 1993.
29. Lister, R. G.: The use of a t-maze to measure anxiety in the mouse. Psychopharmacology (Berlin) 92:180–185; 1987.
30. Litt, M. D.; Babor, R. F.; DelBoca, F. K.; et al.: Types of alcoholics. II. Application of an empirically derived typology to treatment matching. Arch. Gen. Psychiatry 49:609–614; 1991.
31. McKinzie, D. L.; Sajdyk, T. J.; McBride, W. J.; Murphy, J. M.; Lumeng, L.; Li, T.-K.: Acoustic startle and fear-potentiated startle responding in alcohol-preferring (P) and -nonpreferring (NP) lines of rats. Pharmacol. Biochem. Behav. (in press).
32. Meliska, C. J.; Bartke, A.; McGlacken, G.; Jensen, R. A.: Ethanol, nicotine, amphetamine and aspartame consumption and preferences in C57BL/6 and DBA/2 mice. Pharmacol. Biochem. Behav. 50:619–626; 1981.
33. Misslin, R.; Cigrang, M.: Does neophobia necessarily imply fear or anxiety? Behav. Process. 42:45–50; 1986.
34. Misslin, R.; Ropartz, P.; Jung, L.: Impairment of responses to novelty by apomorphine and its antagonism by neuroleptics in mice. Psychopharmacology (Berlin) 82:113–117; 1984.
35. Nicholls, B.; Springham, A.; Mellanby, J.: The playground maze: A new method for measuring directed exploration in the rat. J. Neurosci. Methods 43:171–180; 1992.
36. Patacchioli, F. R.; Taglialatela, G.; Agelucci, L.; Cerbone, A.; Sadile, A. G.: Adrenocorticoid receptor binding in the rat hippocampus: Strain-dependent covariations with arousal and habituation to novelty. Behav. Brain Res. 33:287–300; 1989.
37. Peeler, D. F.; Nowakowski, R. S.: Genetic factors and the measurement of exploratory activity. Behav. Neural Biol. 48:90–103; 1987.
38. Pettit, H. O.; Ettenberg, A.; Bloom, F. E.; Koob, G. F.: Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berlin) 84:167–173; 1984.
39. Piazza, P. V.; Deminiere, J. M.; LeMoal, M.; Simon, H.: Factors that predict individual vulnerability to amphetamine self-administration. Science 24:1511–1513; 1989.
40. Pierce, R. C.; Crawford, C. A.; Nonneman, B. A.; Bardo, T.: Effect of forebrain dopamine depletion on novelty-induced place preference behavior in rats. Pharmacol. Biochem. Behav. 36:321–325; 1990.
41. Robbins, T. W.; Iversen, S. D.: A dissociation of the effects of d-amphetamine on locomotor activity and exploration in rats. Psychopharmacologia 28:155–164; 1973.
42. Robinet, P. M.; Rowlett, J. K.; Bardo, M. T.: Individual differences in novelty-induced activity and the rewarding effects of novelty and amphetamine in rats. Behav. Proces. 44:1–9; 1998.
43. Robinson, T. E.; Camp, D. M.: Does amphetamine preferentially increase the extracellular concentration of dopamine in the mesolimbic system of freely moving rats? Neuropsychopharmacology 3:163–173; 1990.
44. Schwartz, R. M.; Burkhart, B. R.; Green, B.: Turning on or turning off: Sensation seeking or tension reduction as motivation determinants of alcohol use. J. Consult. Clin. Psychol. 46:1144–1145; 1978.
45. Segal, B.; Singer, J. L.: Daydreaming, drug and alcohol use in college students: A factor analytic study. Addict. Behav. 1:227–235; 1976.

46. Spyraki, C.; Fibiger, H. C.; Phillips, A. G.: Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology (Berlin) 79:278–283; 1983.
47. Stewart, R. B.; Gatto, G. J.; Lumeng, L.; Li, T.-K.; Murphy, J. M.: Comparison of alcohol-preferring (P) and nonpreferring (NP) rats on tests of anxiety and for the anxiolytic effects of ethanol. Alcohol 10:1–10; 1993.
48. Wills, T. A.; Vaccaro, D.; McNamara, G.: Novelty seeking, risk taking, and related constructs as predictors of adolescent substance use: an application of Cloninger's theory. J. Subst. Abuse. 6:1–20; 1994.
49. Zuckerman, M.: Sensation seeking: A comparative approach to a human trait. Behav. Brain. Sci. 7:413–471; 1984.
50. Zuckerman, M.: Sensation-seeking: Beyond the optimal level of arousal. Hillsdale, N.J.: Lawrence Erlbaum associates; 1979.