Pharmacology Biochemistry and Behavior, Vol. 59, No. 4, pp. 813–818, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00542-X

Rat Strain Differences in Open-Field Behavior and the Locomotor Stimulating and Rewarding Effects of Amphetamine

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Received 7 July 1997; Accepted 10 September 1997

STÖHR, T., D. SCHULTE WERMELING, I. WEINER AND J. FELDON. *Rat strain differences in open-field behavior and the locomotor stimulating and rewarding effects of amphetamine.* PHARMACOL BIOCHEM BEHAV **59**(4) 813–818, 1998.—Fischer 344 (F344) and Lewis (LEW) rats show considerable neuroanatomical and neurophysiological differences within the mesolimbic dopamine system. The aim of our experiments was to study the functional correlates of such differences by examining open-field behavior and the sensitivity towards the psychostimulant and rewarding effects of amphetamine in male and female, F344 and LEW rats. In addition, the consequences of short versus extended habituation to open-field testing on amphetamine locomotion in these two rat strains was assessed. LEW but not F344 rats irrespective of gender showed between-session habituation of open-field activity. Amphetamine-induced locomotion was higher in F344 compared to LEW rats and in females compared to male rats. In addition, extended habituation increased the locomotor effects of amphetamine. The rewarding effects of amphetamine as measured by the conditioned place preference test were more pronounced in F344 than in LEW rats. Our results suggest that the two rat strains differed in their behavioral response to mild stress and to amphetamine and that these differences may depend upon differences within the mesolimbic dopamine system. © 1998 Elsevier Science Inc.

Fischer rat Lewis rat Amphetamine Open field Conditioned place preference

FISCHER 344 (F344) and Lewis (LEW) rats are frequently used inbred strains of rats. Numerous neuroanatomical and neurochemical studies revealed fundamental strain differences between F344 and LEW rats in a number of brain circuits including the mesolimbic dopamine system—neurons projecting from the ventral tegmental area to the nucleus accumbens. For instance, LEW rats have a fewer number of spontaneously active dopaminergic neurons (22), less neurofilament proteins, and reduced levels of TH and CCK within VTA neurons (16) as well as lower basal release of dopamine, glutamate, and 5-HT in the nucleus accumbens (5,28,33). The mesolimbic dopamine system is a well characterized brain substrate of locomotion, motivation, and stress [see (19) for review]. Therefore, we investigated F344 and LEW rats in three behavioral tests that are known to be at least partially dependent upon mesolimbic dopaminergic transmission, namely novelty-induced locomotion and the psychostimulant and conditioned rewarding effects of amphetamine.

Strain differences in basal locomotor activity were reported by several investigators. However, whereas in one study lower activity of the LEW strain was observed (9), another study reported higher activity of this strain compared to F344 rats (5). One important difference between these studies that might account for the opposite findings relates to the test environments. One study (5) used an open field, whereas the other (9) was performed in activity cages. Because activity cages are often more similar to the home cage and, therefore, less novel to the animals, it is possible that the degree of novelty of the test environment might have influenced the behavioral outcomes. More specifically, we hypothesized that dur-

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ing repeated exposure to a novel environment LEW rats will be more active during initial exposures when the environment is neophobic, but F344 rats will be more active in later exposures, when due to habituation the environment becomes less neophobic (more familiar).

Although there is consistent evidence that F344 rats are more resistant to the behavioral effects of opioids and ethanol than LEW (34,35), strain differences in the effects of psychostimulants have been less well investigated. Locomotor activity following metamphetamine and cocaine was shown to be larger in LEW than in F344 rats (5,13,29), but another study reported no differences in the psychostimulant effects of cocaine (18). We therefore examined the locomotor effects of the prototypical psychostimulant drug amphetamine in the open field in F344 and LEW rats. In addition, in view of the evidence that the psychostimulant effects of certain drugs may depend on the level of previous habituation to the test environment (26) we examined the stimulant effects of amphetamine in rats with different levels of habituation to the open field. If the two rat strains differ in the extent of habituation to the open field then the psychostimulant effects will not only depend on the genetic background and on the extent of previous habituation to the test environment per se, but also show a differential influence of habituation in one vs. the other rat strain.

The psychostimulant theory of addiction (36) postulates that the locomotor stimulant and rewarding effects of addictive drugs are mediated by a common neuronal substrate. One implication of this theory is that the psychostimulant effects of amphetamine might have predictive value for its rewarding effects. In other words, animals that respond more to the stimulant effects of a certain drug (e.g., amphetamine) will also show a higher sensitivity to its rewarding effects as evidenced, for instance, by enhanced place preference conditioning established with the drug. Although there is extensive data supporting this theory, there is also some experimental evidence inconsistent with this view (6). We, therefore, assessed the rewarding properties of amphetamine in LEW and F344 rats using the conditioned place preference paradigm to assess whether there is a relationship between the psychostimulant and the rewarding effects of amphetamine in the two strains.

METHOD

Subjects

Male and female Fischer 344/NHsd and Lewis/SsNHsd rats (Harlan NL) were housed four per cage in standard Macrolon cages under a reversed light–dark cycle (lights off 0700 to 1900 h). At the beginning of the experiment their mean weights were 347 ± 5 (male F344), 368 ± 18 (male LEW), 202 ± 4 (female F344), and 225 ± 4 (female LEW). All rats were extensively handled before the start of the experiment.

Apparatus and Procedures

Open field. The open field consisted of four rectangular boxes (80 × 80 cm) made of gray PVC and located in a dimly illuminated room (12 lx as measured at the bottom of the open-field boxes). A square of 20 × 20 cm in the middle of each open-field box was designated as the center. Open field behavior (locomotor activity, time spent in the center, and latency of the first entry to the center) was measured via a computerized animal observation system (Ethovision, Noldus, NL) that was connected to a camera mounted on the ceiling above the open-field boxes. All animals were brought into the testing room for 30 min before the start of each session for habituation.

Half of the animals (HAB; $n = 4$ per strain and gender) were tested in the open field on 4 consecutive days for 30 min/day, whereas the other half of the animals (non-HAB; $n = 4$ per strain and gender) remained undisturbed in their home cages during this time. On day 5 all animals were tested for 30 min after an injection of saline (1 ml/kg). Immediately afterwards, all rats received an injection of *d*-amphetamine sulphate (1.0 mg/kg IP, Sigma) followed by further testing in the open field for 60 min. We used only a single dose of amphetamine that produces in other strains of rats clear but not maximal psychostimulant effects.

Conditioned place preference. Amphetamine-induced place conditioning was performed in shuttle boxes (30 × 60 × 30 cm w × 1 × h) with a transparent Plexiglas top and wooden walls and housed in a dimly illuminated room. One box was painted black and fitted with a smooth black floor. The other box was white with a textured white floor. For training, the two boxes were separated by a partition that was replaced by a wire mesh central platform (5 × 2 cm w × 1) during preexposure and test sessions. Behavior of the animals (time spent in each of the compartments) was measured via a computerized animal observation system (Ethovision, Noldus, NL), which was connected to a camera mounted on the ceiling above the place conditioning boxes.

The experiment consisted of three stages: Preexposure: all animals (n = 11 per strain and gender) were preexposed for three daily 15-min sessions. The time the animals spent in each of the two compartments was measured on the third day of testing. Animals that displayed preference levels for one compartment larger than 90% were excluded from the experiment. Conditioning: conditioning was done to the less-preferred compartment as determined on the third day of preexposure with either 1.0 mg/kg *d*-amphetamine or 1 ml/kg saline. All animals received vehicle (1 ml/kg saline) before being exposed to the other compartment. One conditioning trial per day and three conditioning trials per compartment were performed in a counterbalanced manner. Test: on the day following the last conditioning trial rats were exposed to the boxes with free access to both compartments and the time they spent in the drug associated compartment was measured.

Statistical Analysis

Open-field data were analyzed using analysis of variance (ANOVA) with main factors of strain (F344/LEW), gender (male/female), and habituation (extended/short) and, where appropriate, with repeated measurements of the factor of time. Place preference conditioning data were analyzed by ANOVA with strain and gender as main factors and preference shift (time spent in drug paired compartment after conditioning minus before conditioning) as the dependent variable.

RESULTS

Open-Field Behavior

Analysis of general locomotor activity across all testing days revealed no significant outcomes, with the effect of gender approaching significance, $F(1, 12) = 4.204$, $p = 0.06$ reflecting a higher activity of female compared with male rats. The same ANOVA with repeated measurements over days (four daily sessions) and intervals (10 3-min intervals per session) revealed interactions of strain × day, $F(3, 36) = 15.383$,

$p < 0.001$, strain × intervals, $F(9, 108) = 2.240$, $p < 0.05$, and strain × days × intervals, $F(27, 324) = 1.764$, $p < 0.05$. As shown in Fig. 1A, LEW rats demonstrated a clear between session habituation, i.e., a reduction of overall activity from day to day, over the four days, while no such phenomenon was observed in F344 rats; in fact, the opposite pattern was evident; namely, an increase in activity from one day to the next. In addition, within-session habituation was faster in LEW rats, as indicated by the fact that LEW rats showed higher activity at the beginning of testing, whereas F344 rats were more active at the end of each open-field exposure (Fig. 1B).

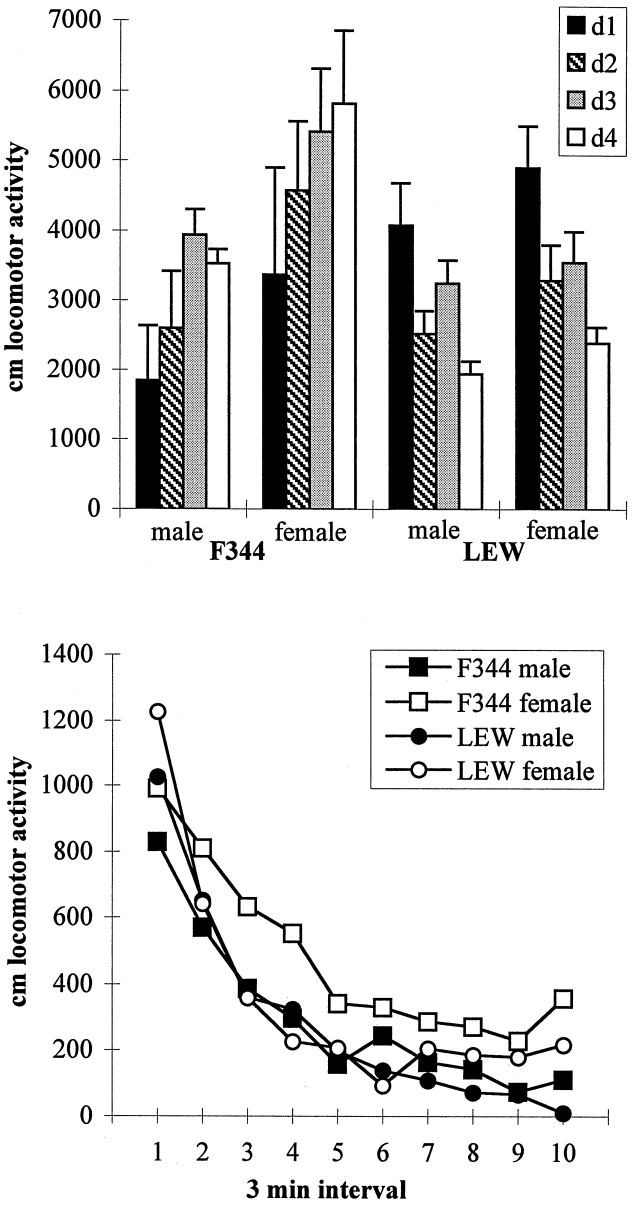


FIG. 1. Basal locomotor activity of male and female F344 and LEW rats in the open field under habituated and unhabituated conditions. The upper panel represents means and standard errors of total distance traveled during four daily 30-min sessions (between-session habituation). The lower panel shows means and standard errors of distance traveled in 10 3-min intervals averaged across the daily four sessions (within-session habituation).

The rate of defecation was significantly different in the two strains, $F(1, 12) = 4.63$, $p = 0.05$, with F344 rats having a higher number of fecal bolis than LEW rats (F344 1.53 ± 0.40; LEW 0.38 ± 0.21). There were no differences in the percentage of time spent by the animals in the center of the open field (all Fs < 1).

Activity Following Saline and Amphetamine Injections

Analysis of locomotor activity following saline injection yielded a significant interaction of strain × habituation, $F(1, 14) = 8.12$, $p < 0.01$. HAB-LEW rats showed less activity compared with non-HAB-LEW, while in F344 rats there was no difference between HAB and non-HAB animals (Fig. 2A).

Analysis of locomotor activity following amphetamine challenge yielded a significant effect of strain, $F(1, 24) = 8.933$, $p < 0.01$, and gender, $F(1, 24) = 19.687$, $p < 0.001$, as well as significant strain × interval, $F(19, 456) = 2.45$, $p < 0.001$, gender × interval, $F(19, 456) = 6.706$, $p < 0.0001$, and habituation × interval interactions, $F(19, 456) = 1.692$, $p < 0.05$. Figure 2B shows that F344 rats displayed an earlier onset and a greater degree of amphetamine hyperactivity. Moreover, the effect of amphetamine on locomotion was larger and more prolonged in female compared to male rats irrespective of strain. Further habituation resulted in an earlier onset of hyperactivity following amphetamine. To account for the differences in basal locomotion, an additional ANOVA was calculated with repeated measurements of the factor of drug (saline vs. amphetamine). In addition to a significant main effect of drug, $F(1, 24) = 115.2$, $p < 0.0001$, significant interactions of drug × strain, $F(1, 24) = 9.3$, $p < 0.01$, drug × gender, $F(1, 24) = 15.9$, $p < 0.001$, and drug × habituation, $F(1, 24) = 4.7$, $p < 0.05$, were found. As is shown in Fig. 2C, amphetamine had clear stimulant effects. This effect of amphetamine was larger in F344 than in LEW rats, in female than in male rats, and in HAB than in non-HAB animals.

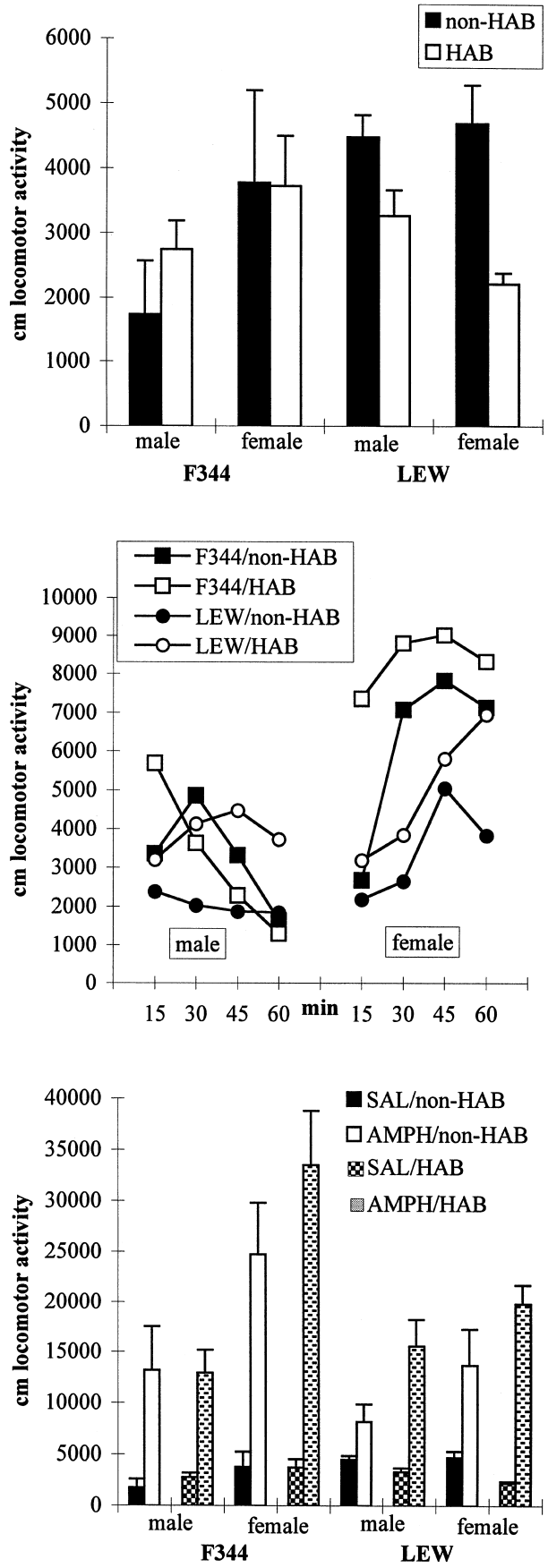
Amphetamine-Induced Place Conditioning

ANOVA with preference shift as a dependent variable and drug (saline/amphetamine), strain (F344/LEW), and gender (male/female) as main factors revealed a significant interaction of drug × strain, $F(1, 41) = 4.1$, $p < 0.05$. As Fig. 3 illustrates, both male and female F344 rats, but not LEW rats of either gender, showed a significant place preference for the drug-associated compartment after amphetamine but not after saline.

DISCUSSION

Our experiments revealed strain and gender differences in open-field behavior (mild stress-induced locomotion) and in the sensitivity to the psychostimulant and rewarding effects of amphetamine. In the open-field test LEW rats exhibited between- and within-session habituation of novelty-induced locomotion, whereas F344 rats showed no between-session and less within-session habituation. These results may at least partially explain the discrepant findings on strain differences in locomotor activity: LEW rats were shown to have higher levels of activity than F344 rats in a large unfamiliar test environment (5), but lower activity in smaller, less neophobic activity boxes (9). Different degrees of familiarity with the test apparatus might have contributed towards these opposite findings.

Locomotor activity in an unfamiliar environment is typically regarded as a behavioral stress response (15). Therefore, habituation of activity in such an environment can be seen as



a form of coping with stressful events. At least two different neuronal systems have been shown to be involved in such habituation to stress. Hooks and Kalivas (17) showed that the mesoaccumbens pallidal circuitry is involved in mediating habituation of locomotor activity in an unfamiliar environment. Given the well-known F344/LEW differences in the mesolimbic dopamine system, these differences might subserve the differential coping response of the two strains to a stressor. In addition, results of Bodnoff et al. (3) suggest that the benzodiazepine receptor system is another brain circuitry involved in habituation to novelty. LEW rats have a higher number of BDZ receptors (30), which may account for the faster habituation in this strain compared to the F344 strain of rats.

In addition to locomotor activity, defecation was assessed as an index of emotionality during open-field exposure. This measure again revealed higher emotionality in F344 rats and is in accordance with additional observations of higher emotionality in several behavioral tests (Stöhr et al., submitted). In a recent report Ramos et al. (24) described rat strain differences in anxiety related behaviors. They found that both F344 and LEW rats displayed the highest levels of anxiety compared with four other inbred strains of rats. However, differences in anxiety between F344 and LEW rats were inconsistent. Whereas, for instance, higher defecation of LEW rats compared with F344 rats was found in the open field, the opposite pattern of strain differences (i.e., lower defecation of LEW rats) was found in the black–white box test. Because of the methodological differences (e.g., one open-field exposure vs. five open-field exposures), it is difficult to compare their results with ours.

Both the open-field and the conditioned place preference tests revealed strain differences in response to amphetamine: LEW rats were less sensitive than F344 rats to the locomotor and rewarding effects of amphetamine. Lower sensitivity to the psychostimulant effects of amphetamine in LEW compared to F344 rats was also found by George et al. (13), although in this case only male rats were examined. This is somewhat surprising, as the LEW strain is known to show higher sensitivity to the locomotor activating and rewarding effects of other psychostimulant drugs such as metamphetamine and cocaine (5,13,18,29). George et al. (13) examined cocaine and amphetamine-induced locomotor activity in several different rat strains including F344 and LEW rats. They found that remarkable strain differences in the locomotor effects of these two psychostimulant drugs exist. However, the strain differences were not consistent for cocaine and amphetamine, i.e., whereas out of four rat strains F344 rats had the highest ED50 for cocaine, this strain had the lowest ED50 for amphetamine-induced locomotor activity. Diverging from other hypotheses [e.g., see (19) for review], these authors conclude that the psychostimulant effects of these two drugs might be at least partially mediated via different brain substrates.

The observed strain differences in the sensitivity towards amphetamine may be due to differences at the level of the hy-

FIG. 2. Locomotor activity following either saline or amphetamine injections in male and female F344 and LEW and HAB and non-HAB rats. The upper panel shows means and standard errors of total distance traveled during 30 min following an injection of saline. The middle panel shows distance traveled in 15-min intervals during 60 min following an injection of amphetamine. The lower panel compares total distance traveled following saline with total distance traveled following amphetamine under habituated and unhabituated conditions.

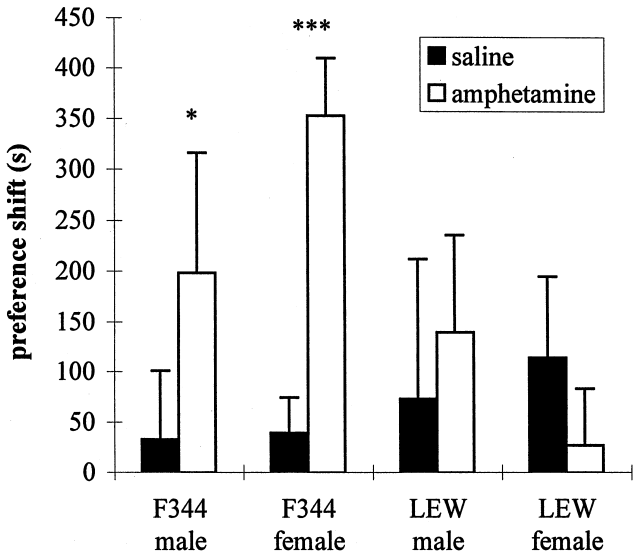


FIG. 3. Amphetamine-induced place conditioning in male and female F344 and LEW rats. This figure represents the means and standard errors of preference shift (difference in time spent in the drug associated compartment after and before conditioning).

pothalamus–pituitary–adrenal system: LEW rats have been shown to exhibit a deficient neuroendocrine response to stress (12,14,25,31,32). For instance, stress- or drug-induced corticosterone release is attenuated in LEW compared to F344 rats (29). An involvement of corticosterone in the psychostimulant effects of amphetamine is suggested by the findings of Cador et al. (4) that the depletion of endogenous corticosterone by adrenalectomy in rats attenuates, whereas the implantation of pellets releasing high amounts of corticosterone potentiates, amphetamine-induced locomotion. Likewise, Piazza and co-workers (20,23) have shown that the sensitivity towards the psychostimulant and reinforcing effects of amphetamine is highly correlated with endogenous corticosterone levels, i.e., rats with a high stress-induced corticosterone release show higher amphetamine-induced locomotion and are more likely to develop amphetamine self-administration. Therefore, it is tempting to speculate that the observed strain differences in the psychostimulant and rewarding effects of amphetamine are at least partially mediated by differences in the hypothalamus–pituitary–adrenal axis between F344 and LEW rats.

Alternatively, the observed strain differences in the sensitivity to the psychostimulant and rewarding effects might be due to strain differences in the pharmacokinetics of amphetamine. In fact, it has been reported (5) that F344 LEW differences exist in the pharmacokinetics of metamphetamine: LEW rats had higher blood and brain concentrations of metamphetamine and amphetamine following an injection of metamphetamine. Therefore, it seems not very probable that F344 rats, following an injection of amphetamine, will have higher blood and brain concentrations of this drug, which might account for their higher sensitivity to amphetamine's psychostimulant and rewarding effects.

Major gender differences in the effects of amphetamine were detected in our experiments: female rats of both strains showed a greater behavioral activation after amphetamine than their male counterparts. Furthermore, place conditioning induced by amphetamine was greater in female F344 rats compared to male F344 rats. This is in line with other findings of enhanced amphetamine-induced locomotion and stereotyped behavior in female rats (21,26,27). In addition, gender differences in the neurochemical effects of amphetamine have been reported such as a potentiated amphetamine-induced dopamine release in the striatum of females (8) or increased amphetamine-induced c-*fos* expression in the dorsal striatum (7). However, a recent review and meta-analysis reviewing several amphetamine place-conditioning experiments revealed no evidence for gender differences in the rewarding properties of amphetamine (1).

Our experiments further showed that extended habituation enhances the effect of amphetamine on locomotor activity. A similar result was obtained by Russell and co-workers (26), who showed stronger amphetamine-induced stereotyped behavior in rats following habituation to the test environment. Surprisingly, an enhanced amphetamine-induced locomotion following extended habituation to the open field was not strain dependent, although habituation of novelty-induced locomotion was found only in the LEW rat strain.

In summary, our results support the view that there exist rat strain differences in the response to mild stress. Furthermore the sensitivity towards the locomotor stimulating and conditioned rewarding effects of amphetamine was dependent upon the genetic background (i.e., rat strain and gender). We hypothesise that two neuronal systems may account for these differences that are well known to contribute to the behavioral effects of stress and amphetamine: the hypothalamus–pituitary–adrenal axis and the mesolimbic dopamine system. Strain and gender differences have been found in both of these systems, with increased responsiveness in female compared with male rats and in F344 compared with LEW rats (2,8,10,11). In parallel, rats with the higher sensitivity within these systems (i.e., female and F344 rats) also showed a larger behavioral response to amphetamine.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Swiss Federal Institute of Technology, ETH Zurich.

REFERENCES

1. Bardo, M. T.; Rowlett, J. K.; Harris, M. J.: Conditioned place preference using opiates and stimulant drugs: A meta-analysis. Neurosci. Biobehav. Rev. 19:39–51; 1995.
2. Blanchard, B. A.; Glick S. D.: Sex differences in mesolimbic dopamine responses to ethanol and relationship to ethanol intake in rats. In: Galanter, M., ed. Women and alcoholism. New York: Plenum Press; 1995:231–241.
3. Bodnoff, S. R.; Suranyi-Cadotte, B. E.; Quirion, R.; Meaney, M. J.: Role of the central benzodiazepine receptor system in behavioral habituation to novelty. Behav. Neurosci. 103:209–212; 1989.
4. Cador, M.; Dulluc, J.; Mormède, P.: Modulation of the locomotor response to amphetamine by corticosterone. Neuroscience 56:981–988; 1993.
5. Camp, D. M.; Browman, K. E.; Robinson, T. E.: The effects of metamphetamine and cocaine on motor behavior and extracellular dopamine in ventral striatum of Lewis versus Fischer 344 rats. Brain. Res. 668:180–193; 1994.

6. Carr, G. D.; Phillips, A. G.; Fibiger, H. C.: Independence of amphetamine reward from locomotor stimulation demonstrated by conditioned place preference. Psychopharmacology (Berlin) 94:221–226; 1988.
7. Castner, S. A.; Becker, J. B.: Sex differences in the effect of amphetamine on immediate early gene expression in the rat dorsal striatum. Brain Res. 712:245–257; 1996.
8. Castner, S. A.; Xiao, L.; Becker, J. B.: Sex differences in striatal dopamine: In vivo microdialysis and behavioural studies. Brain Res. 610:127–134; 1993.
9. Chaouloff, F.; Kulikov, A.; Sarrieau, A.; Castanon, N.; Mormède, P.: Male Fischer 344 and Lewis rats display differences in locomotor reactivity but not in anxiety-related behaviors: Relationship with the hippocampal serotonergic system. Brain Res. 693:169–178; 1995.
10. Chisari, A.; Carino, M.; Perone, M.; Gaillard, R. C.; Spinedi, E.: Sex and strain variability in the rat hypothalamo–pituitary–adrenal (HPA) axis function. J. Endocr. Invest. 18:25–33; 1995.
11. Critchlow, V.; Liebelt, A.; Bar-Sela, M.; Mountcastle, W.; Lipscomb, H. S.: Sex differences in resting pituitary adrenal function in the rat. Am. J. Physiol. 205:807; 1963.
12. Dhabhar, F. S.; McEwen, B. S.; Spencer, R. L.: Stress response, adrenal steroid receptor levels and corticosteroid-binding globulin levels—A comparison between Sprague–Dawley, Fischer 344 and Lewis rats. Brain Res. 616:89–98; 1993.
13. George, F. R.; Porrino, L. J.; Ritz, M. C.; Goldberg, S. R.: Inbred rat strain comparisons indicate different sites of action for cocaine and amphetamine locomotor stimulant effects. Psychopharmacology (Berlin) 104:457–462; 1991.
14. Glowa, J. R.; Gyer, M. A.; Gold, P. W.; Sternberg, E. M.: Differential startle amplitude and corticosterone response in rats. Neuroendocrinology 56:719–723; 1992.
15. Gray, J. A.: The psychology of fear and stress. In: Gray, J. A., ed. Problems in the behavioral sciences. Cambridge University Press; 1987.
16. Harris, H. W.; Nestler, E. J.: Immunohistochemical studies of mesolimbic dopaminergic neurons in Fischer 344 and Lewis rats. Brain Res. 706:1–12; 1996.
17. Hooks, M. S.; Kalivas, P. W.: The role of the mesoaccumbens-pallidal circuitry in novelty-induced behavioral activation. Neuroscience 64:587–597; 1995.
18. Kosten, T. A.; Miserendino, M. J.; Chi, S.; Nestler, E. J.: Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. J. Pharmacol. Exp. Ther. 269:137–144; 1994.
19. Le Moal, M.; Simon, H.: Mesocorticolimbic dopaminergic network: Functional and regulatory roles. Physiol. Rev. 71:155–234; 1991.
20. Marinelli, M.; Piazza, P. V.; Deroche, V.; Maccari, S.; Le Moal, M.; Simon, H.: Corticosterone circadian secretion differentially facilitates dopamine-mediated psychomotor effect of cocaine and morphine. J. Neurosci. 14:2724–2731; 1994.
21. Meyer, E.: Age- and sex-related differences in amphetamine-induced locomotor activity. Fed. Proc. 36:1033; 1977.
22. Minabe, Y.; Emori, K.; Ashby, C. R.: Significant differences in the activity of midbrain dopamine neurons between male Fischer 344 (F344) and Lewis rats: An in vivo electrophysiological study. Life Sci. 56:PL261–PL267; 1995.
23. Piazza, P. V.; Maccari, S.; Deminière, J.; Le Moal, M.; Mormède, P.; Simon, H.: Corticosterone levels determine individual vulnerability to amphetamine self-administration. Proc. Natl. Acad. Sci. USA 88:2088–2092; 1991.
24. Ramos, A.; Berton, O.; Mordede,P.; Chaouloff, F.: A multiple-test study of anxiety-related behaviours in six inbred rat strains. Behav. Brain Res. 85:57–69; 1997.
25. Rivest, S.; Rivier, C.: Stress and interleukin-1-β-induced activation of c-*fos*, NGFI-B and CRF gene expression in the hypothalamic PVN: Comparison between Sprague–Dawley, Fischer-344 and Lewis rats. J. Neuroendocrinol. 6:101–117; 1994.
26. Russell, R. L.; Pihl, R. O.: The effect of dose, novelty, and exploration on amphetamine-produced stereotyped behavior. Psychopharmacology (Berlin) 60:93–100; 1978.
27. Schneider, B. F.; Norton, S.: Circadian and sex differences in hyperactivity produced by amphetamine in rats. Physiol. Behav. 22:47–51; 1979.
28. Selim, M.; Bradberry, C. W.: Effect of ethanol on extracellular 5-HT and glutamate in the nucleus accumbens and prefrontal cortex: Comparison between the Lewis and Fischer 344 rat strains. Brain Res. 716:157–164; 1996.
29. Simar, M. R.; Saphier, D.; Goeders, N. E.: Differential neuroendocrine and behavioural response to cocaine in Lewis and Fischer rats. Neuroendocrinology 63:93–100; 1996.
30. Smith, C. C.; Hauser, E.; Renaud, N. K.; Leff, A.; Aksentijevich, S.; Chrousos, G. P.; Wilder, R. L.; Gold, P.W.; Sternberg, E. M.: Increased hypothalamic [3H]flunitrazepam binding in hypothalamic–pituitary–adrenal axis hyporesponsive Lewis rats. Brain Res. 569:295–299; 1992.
31. Sternberg, E. M.; Hill, J. M.; Chrousos, G. P.; Kamilaris, T.; Listwak, S. J.; Gold, P. W.; Wilder, R. L.: Inflammatory mediator-induced hypothalamic–pituitary–adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. Proc. Natl. Acad. Sci. USA 86:2374–2378; 1989.
32. Sternberg, E. M.; Young, W. S.; Bernardini, R.; Calogero, A. E.; Chrousos, G. P.; Gold, P. W.; Wilder, R. L.: A central nervous system defect in biosynthesis of corticotropin-releasing hormone is associated with susceptibility to streptococcal cell wall-induced arthritis in Lewis rats. Proc. Natl. Acad. Sci. USA 86:4771–4775; 1989.
33. Strecker, R. E.; Eberle, W. F.; Ashby, C. R., Jr.: Extracellular dopamine and its metabolites in the nucleus accumbens of Fischer and Lewis rats: Basal levels and cocaine-induced changes. Life Sci. 56:PL135–PL141; 1995.
34. Suzuki, T.; George, F. R.; Meisch, R. A.: Differential establishment and maintenance of oral ethanol reinforced behavior in Lewis and Fischer 344 inbred rat strains. J. Pharmacol. Exp. Ther. 245:164–170; 1988.
35. Suzuki, T.; George, F. R.; Meisch, R. A.: Etonitazene delivered orally serves as a reinforcer for Lewis but not Fischer 344 rats. Pharmacol. Biochem. Behav. 42:579–586; 1992.
36. Wise, R. A.; Bozarth, M. A.: A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492; 1987.