Pharmacology Biochemistry and Behavior, Vol. 60, No. 2, pp. 499–505, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(98)00007-0

Dopaminergic Parameters During Social Isolation in Low- and High-Active Mice

OLAF RILKE, MONIKA JÄHKEL AND JOCHEN OEHLER

Laboratory of Neurobiology, Department of Psychiatry, Technical University Dresden, Dresden, Germany

Received 15 August 1997; Revised 12 December 1997; Accepted 12 December 1997

RILKE, O., M. JÄHKEL AND J. OEHLER. *Dopaminergic parameters during social isolation in low- and high-active mice.* PHARMACOL BIOCHEM BEHAV **60**(2) 499–505, 1998.—Alterations induced by social isolation (1 day to 18 weeks) in low- and high-active mice (LAM and HAM) were studied in respect to locomotor activity, [3H]-spiperone binding in the striatum, striatal, and cortical dopamine metabolism, and presynaptic dopaminergic sensitivity to apomorphine (0.75 mg/kg; IP). Isolated HAM and LAM showed increased locomotor activity compared to group-housed mice after long-term isolation (6–18 weeks). Considering the studied dopaminergic parameters, it has been found that social isolation did not affect striatal D2 receptors, striatal and cortical dopamine metabolism, and apomorphine-mediated reduction of dopaminergic metabolism. The change of housing conditions was generally associated with an increase of cortical dopamine metabolism after 1 week. Activity type specific differences in group-housed LAM and HAM were found in the basal striatal dopamine metabolism and in the sensitivity of the nigrostriatal system to autoreceptor activation. The reduced striatal dopamine metabolism and the higher presynaptic sensitivity of HAM may be related to their high active running wheel behavior. © 1998 Elsevier Science Inc.

Social isolation Dopamine metabolism D_2 receptor Apomorphine Mice

THE differential housing of mice, i.e., group and isolated housed, produces differences in the locomotor activity (6,25) and in the behavioral sensitivity to dopaminergic acting drugs (12,25). Isolation induced hyperactivity (6,17,25,26) and enhanced responses to amphetamine as well as to apomorphine (10,25) have been shown in rats and mice suggesting differences in dopaminergic systems between differential-housed animals. However, neurochemical evidences for dopaminergic changes in isolates have been obtained in rats but not in mice. An increase in striatal and a decrease in cortical dopamine metabolism were found in isolated rats (2,16). Receptor binding studies have shown a decrease of striatal dopamine D_2 receptors in isolated rats, possibly resulting from a striatal dopaminergic hyperactivity (1,14). Isolation of mice (4–5 weeks) did not produce any significant alterations in striatal dopaminergic systems as reported in rat experiments (6,25). First, our studies are aimed at reinvestigating dopaminergic systems (dopamine metabolisms in striatum and cortex, striatal dopamine D_2 receptor, presynaptic dopaminergic receptor sensitivity) in dependence on differential housing from 1 day up to 18 weeks. Second, the investigations were done with selected mice according to their running wheel activity. Pharmacological studies with high active (HAM) and low active mice (LAM) have shown differences concerning the nigrostriatal and/or mesolimbic dopaminergic mechanisms (20). To elucidate possible neurochemical mechanisms underlying these observed different dopaminergic responses, pre- and postsynaptic dopaminergic parameters have been studied in isolated and group-housed HAM and LAM.

METHOD

Animals and Housing

The experiments were performed with male NMRI mice (breeder: Hirsch, Heidenau, Germany), which were 5–6 weeks old at the beginning of the test. The animals were kept in controlled environment at 21 ± 2°C and 40–60% air humidity in a 12 L:12 D cycle with food and water ad lib.

We used low- and high-active mice (LAM and HAM) to study how endogenous disposition influences isolation-induced alterations. Mice were differentiated by their running-wheel activity (1 h) according to Jähkel et al. (9).

Eight LAM or HAM, each, were housed in groups or in isolation for 1 day, 1 week, or 3, 6, 12, and 18 weeks.

Requests for reprints should be addressed to Olaf Rilke, AG Neurobiologie, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Technische Universität Dresden, Fetscherstraβe 74, D-01307 Dresden, Germany.

Drug Treatments

Mice were injected with 0.75 mg/kg (IP) apomorphine, a mixed D_1/D_2 receptor agonist (24), followed in 5 min with locomotor activity measurements and decapitation. Control groups were injected with 0.9% saline.

Locomotor Activity Measurements

Locomotion parameters were measured in Plexiglas boxes (60 × 30 × 20 cm high) with eight and four photocell beams located across the long and the short axis for 10 min. Openfield activity was measured by the frequency of beam interruptions and recorded on digital counters. Experiments were performed during the light phase (0900–1200 h).

Chemicals

[^{3}H]-Spiperone (23,5 Ci/mmol) was purchased from Amersham Buchler (Braunschweig, Germany). Other compounds were obtained as follows: bovine serum albumin, 1-heptanesulfonic acid, homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), dopamine, (−)sulpiride, and polyethylenimine from Sigma Chemical Co. (St. Louis, MO) and $CaCl_2$, citric acid, methanol, Na_2EDTA and sodium acetate from Merck (Darmstadt, Germany).

D_2-Receptor Binding Studies

Following decapitation striatum was dissected, frozen in liquid nitrogen, and stored at −70°C until use. Thawed tissues were homogenized (10 strokes with a glass-teflon homogenizer, 1000 turns per min) in 10 ml 50 mM Tris-HCl, pH 7.4, and centrifuged for 10 min at 40,000 × *g*. The resulting pellets were washed twice and rehomogenized in 50 mM Tris-HCl, 120 mM NaCl, pH 7.4, with a final tissue concentration of 8 mg orginal wet weight per ml. Binding assays were performed using 0.1-ml aliquots (equivalent to 25–30 mg striatum protein). [^{3}H]-Spiperone was used as the radioligand for labeling dopamine D_2 receptors in mice striatal preparations (21). The membranes were incubated in 3 ml of 50 mM Tris-HCl, 120 mM NaCl, pH 7.4, including six concentrations (0.01–0.3 nM) of [^{3}H]spiperone at 23°C for 90 min. Nonspecific binding was defined in the presence of 10 μM (−)sulpiride.

All incubations were stopped by rapid filtration with a cell harvester through GF/B filters (presoaked in 0.1% polyethylenimine) under reduced pressure. The filters were washed twice with 4-ml ice-cold 50 mM Tris-HCl, pH 7.4, and radioactivity was determined by means of liquid scintillation counter. Analysis of binding data was performed according to Scatchard (19).

Protein content was measured with Bradford's method (4) using bovine serum albumin as the standard.

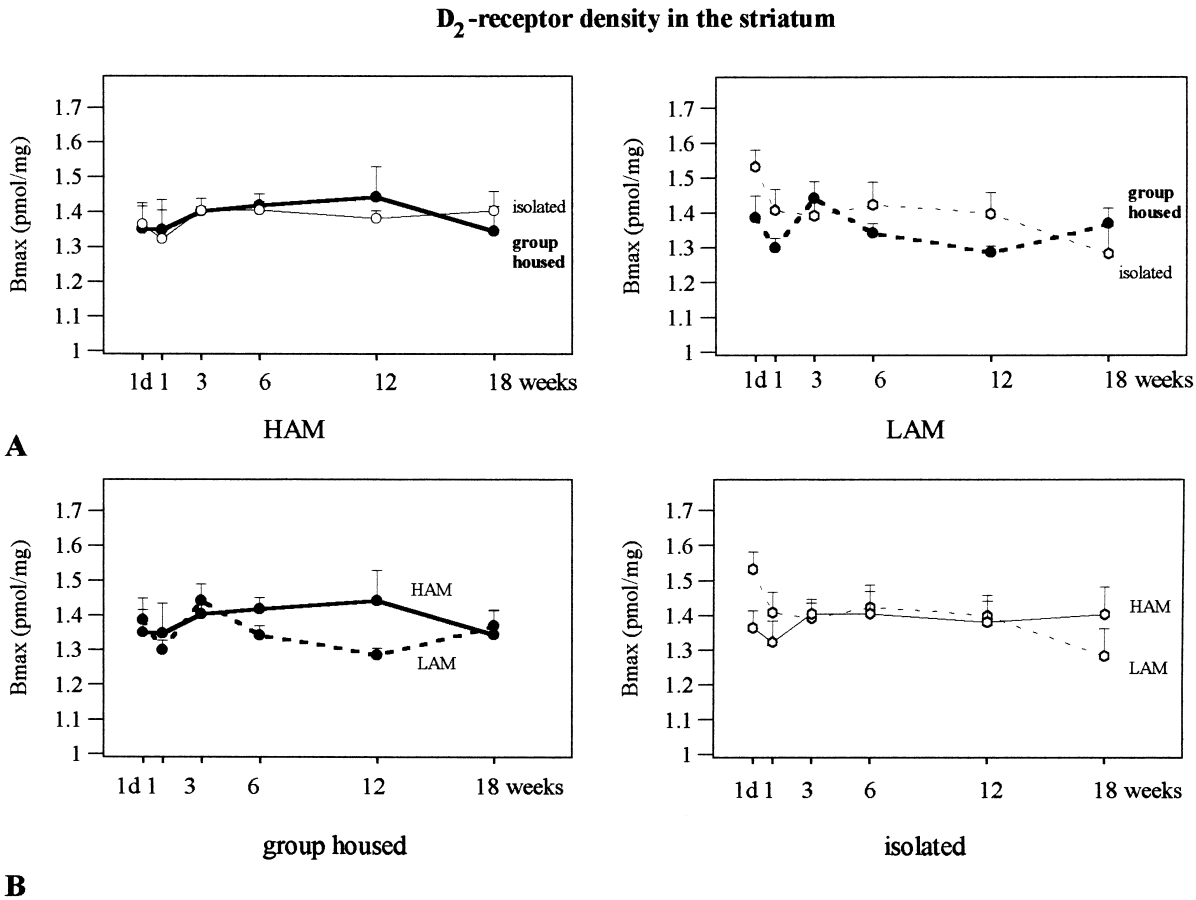

FIG. 1. (A) Striatal D_2 receptor densities in differentially housed HAM (solid line) and LAM (broken line) in the time course from 1 day up to 18 weeks. (B) Striatal D_2 receptor densities of high-active (HAM—solid line) and low-active mice (LAM—broken line) after 1 day up to 18 weeks housing in groups (filled symbols) and individual housing (open symbols), respectively. Error bars indicate SEM (n = 8).

HPLC Analyses

Decapitated animals' striatum and cortex were rapidly dissected, frozen in liquid nitrogen, and stored at −70°C until use. The tissues were weighed and then ultrasonically homogenized in 0.1 M perchloric acid. Following centrifugation at 14,000 × *g* for 15 min the supernatant was directly injected onto the HPLC column (C18 Ultrasphere, 75 3 4.6 mm, 3-mm particle size). The mobile phase consisted of 0.02 M sodium acetate/0.0125 M citric acid buffer, pH 3.7, containing 8% (v/v) methanol, 0.042% heptanesulfonic acid, and 0.1 mM Na_2 EDTA. The flow-rate was set to 1 ml/min, and the temperature maintained at 31°C. Dopamine, HVA, and DOPAC were electrochemically detected using a working potential of 840 mV. Detection limits based on a signal-to-noise ratio of 3 were 0.5 ng/ml for dopamine, HVA, and DOPAC. Intra- and interassay variability has been estimated to be 2.0–3.7% and 4.5–5.2%, respectively.

Statistical Analysis

Values reported are means ± SEM. The data were tested for homogeneity of variance between groups and then three-way ANOVA (factor 1: housing condition, factor 2: activity type, factor 3: housing time) or four-way ANOVA (factor 4: apomorphine teatment) was performed. Post hoc comparisons by Student's *t*-test were carried out when ANOVA showed statistically significant differences. A level of probability <0.05 was accepted as statistically significant. Statistical tests were performed using SPSS for MS Windows 6.1. (SPSS GmbH Software, München, Germany).

RESULTS

Striatal D_2-Receptors

Three-way ANOVA of [^{3}H]-spiperone affinity to striatal D_2-receptors (K_d) indicated no effects of housing, $F(1, 160) = 1.4$, $p = 0.24$, and activity type, $F(1, 160) = 0.8$, $p = 0.37$.

Differential housing of HAM and LAM from 1 day to 18 weeks did not influence the density of [^{3}H]-spiperone binding sites (B_{max}) in the striatum, $F(1, 160) = 0.97$, $p = 0.33$, as shown in Fig. 1A. Differences in B_{max} values between HAM and LAM were found neither in group-housed nor in individually housed mice, $F(1, 160) = 1.0$, $p = 0.28$ (Fig. 1B). However, a tendentious decrease of B_{max} value (90%) were found in LAM after 12 weeks of group housing.

Open-Field Activity

Isolated HAM and LAM were significant more active than group-housed mice after long-term isolation, $F(1, 360) = 7.8$, $p < 0.01$. Apomorphine (0.75 mg/kg, IP) significantly decreased the open-field activity of differentially housed HAM

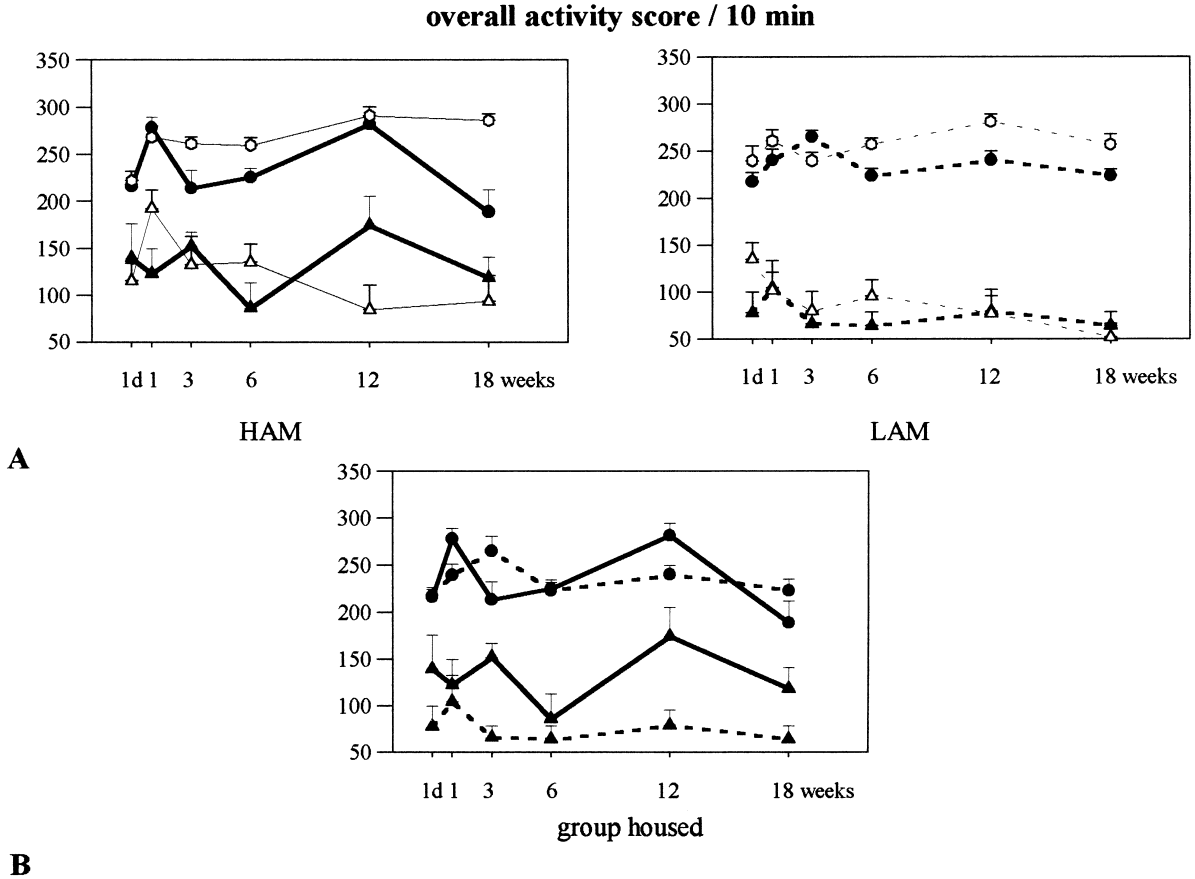

FIG. 2. (A) Open-field activity of group-housed (filled symbols) and isolated-housed (open symbols) HAM and LAM, respectively, after treatment with 0.75 mg/kg, IP, apomorphine (triangles), and 0.9% saline (circles). (B) Reduction of group housed HAM's (solid line) and LAM's (broken line) open-field activity after treatment with 0.75 mg/kg, IP, apomorphine (triangles) in comparison with saline treatment (circles). Mice were differentially housed from 1 day up to 18 weeks. Error bars indicate SEM ($n = 8$).

and LAM (Fig. 2A). By ANOVA analyses, there were no effects of housing on the response to apomorphine, $F(1, 360) = 3.9$, $p = 0.06$, but differences in the drug response between HAM and LAM, $F(1, 360) = 17.1$, $p < 0.001$. Analyses of the drug responses revealed an increased sensitivity to apomorphine of group-housed LAM in comparison to group-housed HAM during the time course of grouped housing (Fig. 2B).

Dopamine Metabolism in the Striatum and the Cortex

Apomorphine (0.75 mg/kg, IP) significantly decreased the ratio of HVA and dopamine in the striatum of differentially housed HAM and LAM (Fig. 3A), resulting from a decrease of HVA and increase of dopamine content, respectively (data not shown). Four-way ANOVA indicated no effects of housing, $F(1, 360) = 2.9$, $p = 0.09$, and activity type, $F(1, 360) = 2.7$, $p = 0.11$, on striatal dopamine metabolism as well as on concentrations of dopamine and HVA. Significant differences of apomorphine response in dependence on housing conditions and activity type were not observed. However, there was a significant interaction of housing and activity type, $F(1, 360) = 3.8$, $p < 0.05$, and differences between LAM and HAM were detected in group-housed mice (Fig. 3B). After 12 and 18 weeks of group housing LAM have an increased ratio of HVA and dopamine compared to HAM [housing time and type: $F(5, 92) = 2.6$, $p < 0.05$]. In this housing condition HAM showed a stronger apomorphine-induced decrease of dopamine metabolism in the striatum, $F(1, 92) = 6.2$, $p < 0.05$.

Four-way ANOVA of dopamine index (HVA/dopamine) in the cortex indicated significant effects of apomorphine, $F(1, 362) = 34.4$, $p < 0.001$, and housing, $F(1, 362) = 8.2$, $p < 0.01$, but no effects of activity type, $F(1, 362) = 0.5$, $p = 0.48$. Apomorphine (0.75 mg/kg, IP) decreased cortical dopamine metabolism independent on housing condition and activity type (Fig. 4A). Between 1 day and 1 week a strong increase (up to 200%) of the dopamine index was found in the cortex, especially in group-housed HAM. A transient reduced cortical dopamine index was found in isolated LAM and HAM after 12 weeks. Similar results were obtained by analyses of cortical DOPAC and dopamine ratios shown in Fig. 4B. Significant effects were found for apomorphine, $F(1, 363) = 76.6$, $p < 0.001$, and housing, $F(1, 362) = 4.1$, $p < 0.05$, but not for activity type, $F(1, 362) = 0.3$, $p = 0.58$. Housing time-dependent increases changes were also detected after 1 week, resulting from a significant decrease of dopamine content (data not shown).

DISCUSSION

The increased locomotor activity found in isolated HAM and LAM has been reported in mice and rats by several other investigators (6,17,25,26). We also found a reduction in spontaneous motor activity by 0.75 mg/kg (IP) apomorphine that is

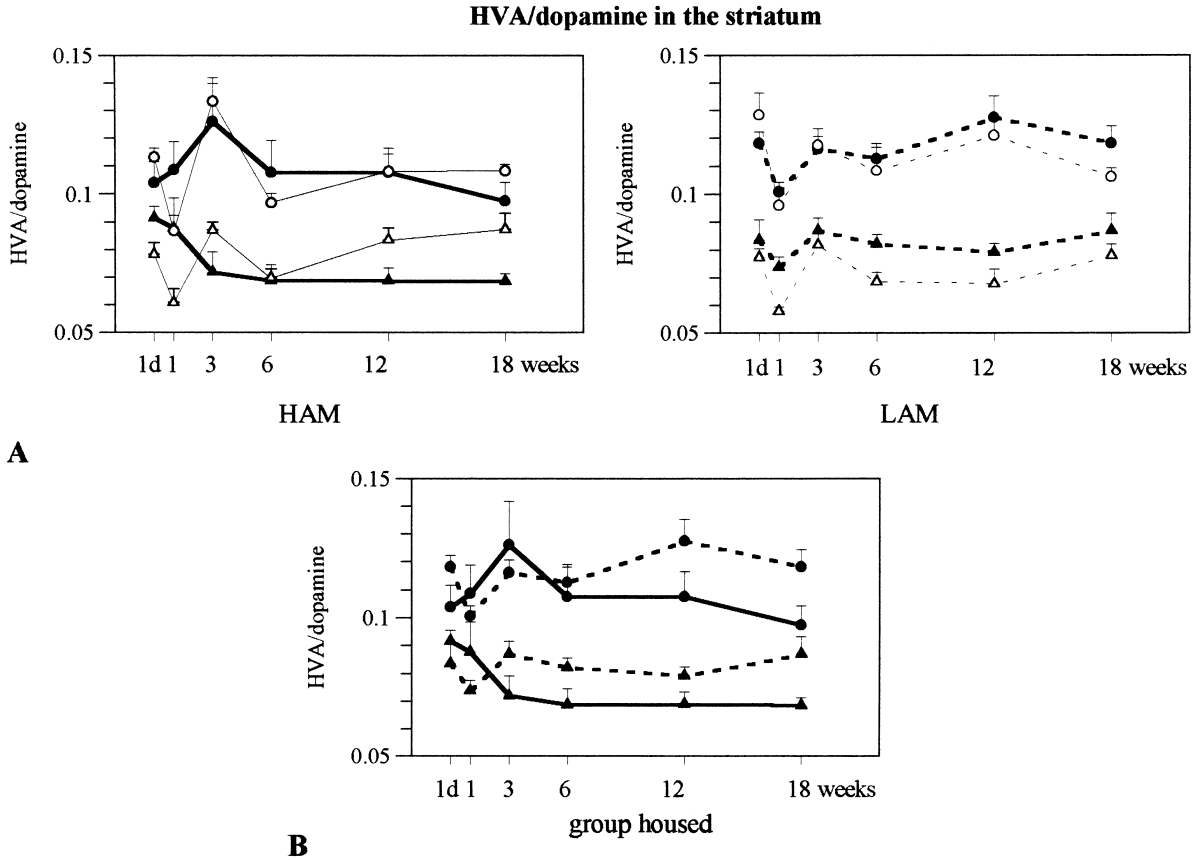

FIG. 3. (A) Striatal dopamine metabolism (HVA/dopamine) of group-housed (filled symbols) and isolated-housed (open symbols) HAM and LAM, respectively, after treatment with 0.75 mg/kg, IP, apomorphine (triangles), and 0.9% saline (circles). (B) Striatal dopamine metabolism of group-housed HAM (solid line) and LAM (broken line) after treatment with 0.75 mg/kg, IP, apomorphine (triangles) in comparison with saline treatment (circles). Mice were differentially housed from 1 day up to 18 weeks. Error bars indicate SEM ($n = 8$).

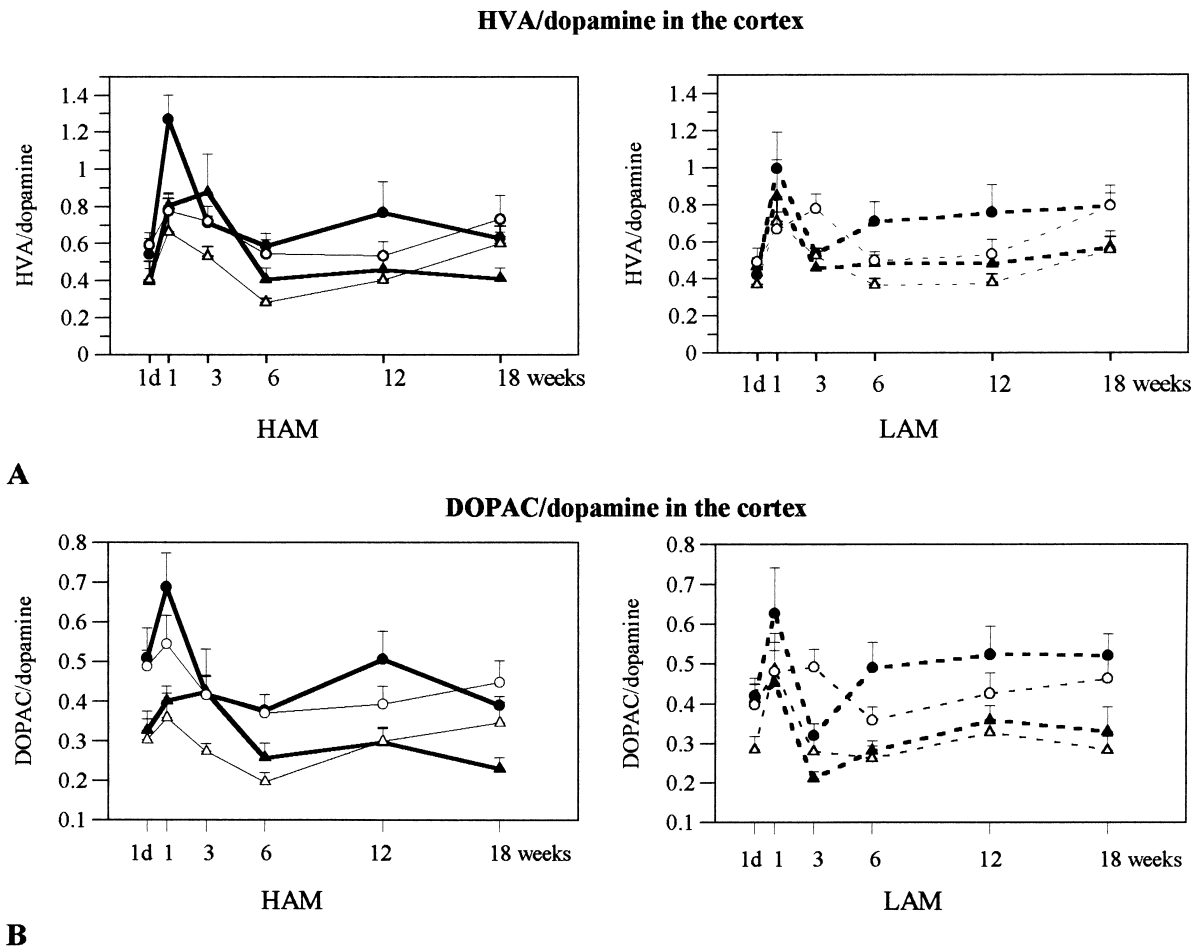

FIG. 4. (A,B) Cortical dopamine metabolism (A: HVA/dopamine; B: DOPAC/dopamine) of group-housed (filled symbols) and isolated-housed (open symbols) HAM and LAM, respectively, after treatment with 0.75 mg/kg, IP, apomorphine (triangles), and 0.9% saline (circles). Mice were differentially housed from 1 day up to 18 weeks. Error bars indicate SEM (n = 8).

believed to reflect the activation of presynaptic D_2-receptors (8). In this behavioral test of presynaptic dopamine receptor sensitivity we observed no effect of differential housing. However, studies in mice and rats have shown enhanced sedative effect of presynaptic doses of apomorphine in isolates (10,25). One reason for this discrepancy may be the higher dose of apomorphine used in the current study.

Studies in rats have shown that social isolation is associated with a decrease in the density of striatal dopamine D_2-receptors (1,14). We found striatal dopaminergic alterations neither in striatal D_2 receptors nor in striatal dopamine metabolism in mice. However, these findings are consistent with other studies in mice (6,25). Thus, we suggest, that striatal dopaminergic alterations are rat-specific responses on social isolation. On the other hand, we found a transient reduction of cortical dopamine metabolism in isolated mice after 12 weeks, which is consistent with studies in rats (2,10,16). In our model of different housing from 1 day up to 18 weeks we were able to detect a strong increase of dopamine metabolism between 1 day and 1 week of group- and isolated-housed mice. Because some studies have consistently reported that psychological stress, such as conditioned fear stress, selectively activates the cortical dopaminergic system (7,11), the increase of cortical dopamine metabolism between 1 day and 1 week might be related to a stress response on novel housing conditions. Interestingly, the stress response is observed in both isolated- and grouped-housed mice and is restricted to 1 week after a change of housing conditions.

Considering the studied dopaminergic parameters, it may be suggest that social isolation of mice does not affect striatal D_2 receptors, dopamine metabolism, and apomorphine-mediated reduction of striatal and cortical dopamine metabolism. The change of housing conditions (in isolated as well as in group housing conditions) is associated with a stress-induced increase of cortical dopamine metabolism after 1 week. Tendencies of reduced cortical dopamine metabolism were found after 12 weeks in isolated mice, but could, of course, depend on changes in neurotransmitter systems, such as serotonergic, glutamatergic, and GABAergic systems, that modulate the cortical dopamine metabolism (8). In a recent study we have shown in mice pre- and postsynaptic serotonergic alterations in the time course of social isolation (15). Functionally, there are close connections between dopaminergic and serotonergic systems in the CNS (18). This is also reflected in the ability of specific serotonin receptor agonists to modulate dopaminergic activity (3,5,13).

Behavioral pharmacological studies with LAM and HAM have shown differences concerning the nigrostriatal and/or

mesolimbic dopaminergic mechanisms (20). Although apomorphine mainly stimulated the climbing activity in HAM, bromocriptine (climbing activity) and amphetamine (locomotion) had stronger effects in LAM. To elucidate possible neurochemical mechanisms underlying these observed different dopaminergic responses, [^{3}H]-spiperone binding sites in the striatum and dopamine metabolism in the striatum and the cortex have been studied. However, we did not find differences in density and affinity of [^{3}H]-spiperone binding sites in the striatum between LAM and HAM. Only tendencies of higher synaptic density of striatal dopamine D_2 receptors of group-housed HAM have been detected after 12 weeks compared to group-housed LAM. Thus, striatal D_2 receptors alone could not be related to the higher climbing activity reported in HAM after apomorphine treatment. It is known that concurrent stimulation of both D_1 and D_2 receptors is required for apomorphine-induced behavioral changes such as stereotypy, rearing, and climbing (8,23). Hence, differences in D_1 receptor sensitivity have to be considered in different behavioral responses between HAM and LAM to apomorphine. Alternatively, the radioligand binding technique may not be sensitive to more subtle changes in receptor sensitivity or heterogeneity.

Activity type-specific differences in the cortical dopamine metabolism were not found, but group-housed HAM have reduced striatal dopamine metabolism compared to group-housed LAM after 12 and 18 weeks. These differences were not detected between isolated HAM and LAM. In isolated mice, dopaminergic activities may be covered by isolation-induced serotonergic alterations. Serotonin is thought to have a tonic inhibitory influence on striatal dopaminergic systems (5), and it was recently demonstrated that serotonergic systems of HAM are strongly reduced by social isolation compared to LAM (15).

After treatment with presynaptic apomorphine dose (0.75 mg/kg) group-housed HAM showed a stronger decrease of striatal dopamine metabolism, suggesting a higher sensitivity of HAM to autoreceptor activation. These findings are not consistent with the locomotor activity response to apomorphine. In the locomotor activity test we found an increased sensitivity to apomorphine of group-housed LAM in comparison to group-housed HAM. Thus, additional biochemical mechanisms besides presynaptic dopamine receptors have to be suggested in the apomorphine-induced hypolocomotion. Indeed, it has been suggested that dopamine agonist-induced hypolocomotion would be mediated by stimulation of particular postsynaptic dopamine receptor populations whose sensitivity to dopaminergic agents would be considerably higher than the sensitivity to the postsynaptic dopamine receptors mediating stereotyped behavior (22).

In summary, the present studies indicate that differential housing of mice did not influence [^{3}H]-spiperone binding sites in the striatum, dopamine metabolism in the striatum and the cortex, and the biochemical response to a presynaptic active apomorphine dose. Differences between activity types were detected in striatal dopamine metabolism. A reduced dopamine metabolism and a higher presynaptic sensitivity to apomorphine (0.75 mg/kg; IP) were found in group-housed HAM compared to grouped-housed LAM that may be related to the type-specific running-wheel behavior.

ACKNOWLEDGEMENTS

This work was supported by BMBF 0316920A.

REFERENCES

1. Bean, G.; Lee, T.: Social isolation and cohabitation with haloperidol-treated partners: Effect on density of striatal dopamine D_2 receptors in the developing rat brain. Psychiatr. Res. 36:307–317; 1991.
2. Blanc, G.; Herve, D.; Simon, H.; Lisoprawski, A.; Glowinski, J.; Tassin, J. P.: Response to stress of mesocortical-frontal dopaminergic neurons in rats after long-term social isolation. Nature 284:265–267; 1980.
3. Boulenguez, P.; Rawlins, J. N. P.; Chauveau, J.; Joseph, M. H.; Mitchell, S. N.; Gray, J. A.: Modulation of dopamine release in the nucleus accumbens by 5-HT_1B agonists: Involvement of the hippocampo-accumbens pathway. Neuropharmacology 35:1521–1529; 1996.
4. Bradford, M. M.: A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal. Biochem. 72:248–254; 1976.
5. Dewey, S. L.; Smith, G. S.; Logan, J.; Alexoff, D.; Ding, Y.-S.; King, P.; Pappas, N.; Brodie, J. D.; Ashby, C. R., Jr.: Serotonergic modulation of striatal dopamine measured with positron emission tomography (PET) and in vivo microdialysis. J. Neurosci. 15:821–829; 1995.
6. Hilakivi, L. A.; Ota, M.; Lister, R. G.: Effect of isolation on brain monoamines and the behavior of mice in tests of exploration, locomotion, anxiety and behavioral despair. Pharmacol. Biochem. Behav. 33:371–374; 1989.
7. Inoue, T.; Tsuchiya, K.; Koyama, T.: Regional changes in dopamine and activation with various intensity of physical and psychological stress in the rat brain. Pharmacol. Biochem. Behav. 49: 911–920; 1994.
8. Jackson, D. M.; Westlind-Danielsson, A.: Dopamine receptors: Molecular biology, biochemistry and behavioural aspects. Pharmacol. Ther. 64:291–369; 1994.
9. Jähkel, M.; Oehler, J.; Schumacher, H.-E.: Influence of nootropic and antidepressive drugs on open field and running wheel behavior in spontaneously high and low active mice. Pharmacol. Biochem. Behav. 49:263–269; 1994.
10. Jones, G. H.; Hernandez, T. D.; Kendall, D. A.; Marsden, C. A.; Robbins, T. W.: Dopaminergic and serotonergic function following isolation rearing in rats: Study of behavioural responses and postmortem and in vivo neurochemistry. Pharmacol. Biochem. Behav. 43:17–35; 1992.
11. Kaneyuki, H.; Yokoo, H.; Tsuda, A.; Yoshida, M.; Mizuki, Y.; Yamada, M.; Tanaka, M.: Psychological stress increases dopamine turnover selectively in mesoprefrontal dopamine neurons of rats: Reversal by diazepam. Brain Res. 557:154–161; 1991.
12. Oehler, J.; Jähkel, M.; Schmidt, J.: The dynamic of transmitter-related changes by social isolation of mice. Zool. Jb. Physiol. 89:289–299; 1985.
13. Parsons, L. H.; Weiss, F.; Koob, G. F.: Serotonin$_1$B receptor stimulation enhances dopamine-mediated reinforcement. Psychopharmacology (Berlin) 128:150–160; 1996.
14. Rilke, O.; May, T.; Oehler, J.; Wolffgramm, J.: Influences of housing conditions and ethanol intake on binding characteristics of D_2, 5-HT_1A, and benzodiazepine receptors of rats. Pharmacol. Biochem. Behav. 52:23–28; 1995.
15. Rilke, O.; Jähkel, M.; Oehler, J.: Dynamic alterations of serotonergic metabolism and receptors during social isolation of low and high active mice. Pharmacol. Biochem. Behav. 59:891–896; 1998.
16. Robbins, T. W.; Jones, G. H.; Wilkinson, L. S.: Behavioural and neurochemical effects of early social deprivation in the rat. J. Psychopharmacol. 10:39–47; 1996.
17. Sahakian, B. J.; Robbins, T. W.; Morgan, M. J.; Iversen, S. D.: The effects of psychomotor stimulants on stereotype and locomo-

tor activity in socially deprived and control rats. Brain Res. 84: 195–205; 1975.
18. Saito, H.; Matsumoto, M.; Tagashi, H.; Yoshioka, M.: Functional interaction between serotonin and other neuronal systems: Focus on in vivo microdialysis studies. Jpn. J. Pharmacol. 70:203–225; 1996.
19. Scatchard, G.: The attractions of proteins for small molecules and ions. Ann. NY Acad. Sci. 51:660–672; 1949.
20. Schumacher, H.-E.; Oehler, J.; Jähkel, M.: Individual motor activity relationships to dopaminergic responses. Pharmacol. Biochem. Behav. 48:839–844; 1994.
21. Seeman, P.; Ulpian, C.; Wregett, K. A.; Wells, J. W.: Dopamine receptor parameters detected by [^{3}H]spiperone depend on tissue concentration: Analysis and examples. J. Neurochem. 43:221–235; 1984.
22. Ståhle, L.; Ungerstedt, U.: Yawning and suppression of exploration in amphetamine-treated rats: Incompatibility with the autoreceptor hypothesis. Psychopharmacology (Berlin) 97:553–560; 1989.
23. Starr, B. S.; Starr, M. S.: Differential effects of dopamine D_1 and D_2 agonists and antagonists on velocity of movements, rearing and grooming in the mouse. Neuropharmacology 25:445–453; 1986.
24. Stoff, J. C.; Kebabian, J. W.: Two dopamine receptors: Biochemistry, physiology and pharmacology. Life Sci. 35:2281–2296; 1984.
25. Wilmot, C. A.; Vander Wende, C.; Spoerlein, M. T.: Behavioral and biochemical studies of dopamine receptor sensitivity in differentially housed mice. Psychopharmacology (Berlin) 89:364–369; 1986.
26. Wright, I. K.; Ismail, H.; Upton, N.; Marsden, C. A.: Effect of isolation-rearing on 5-HT agonist responses in the rat. Psychopharmacology (Berlin) 105:259–263; 1991.