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Dynamic Alterations of Serotonergic Metabolism and Receptors During Social Isolation of Low- and High-Active Mice

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RILKE, O., D. FREIER, M. JÄHKEL AND J. OEHLER. *Dynamic alterations of serotonergic metabolism and receptors during social isolation of low- and high-active mice.* PHARMACOL BIOCHEM BEHAV **59**(4) 891–896, 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 serotonin metabolism, [^{3}H]-8-OH-DPAT binding of presynaptic (midbrain), postsynaptic (hippocampus) 5-HT_{1A} receptors and [^{3}H]-ketanserin binding of cortical 5-HT_{2A} receptors. Individual housing of mice was associated with reduction of serotonin metabolism, depending on isolation time and brain structure. Whereas a transient decrease in the striatum and cortex was detected between 1 week and 6 weeks, reduction of cerebellar and hippocampal serotonin metabolism was found later (12–18 weeks). Serotonergic systems of HAM were found to be more reactive to environmental disturbances, and their serotonin metabolism was more affected by social isolation. Isolation-induced upregulation of cortical 5-HT_{2A} receptors was measured only in HAM. Densities of postsynaptic 5-HT_{1A} receptors in the hippocampus did differ either in grouped or isolated mice. However, there were significant differences in hippocampal 5-HT_{1A} receptor affinity, especially between 1 day and 3 weeks. Transient downregulation of presynaptic 5-HT_{1A} receptors in the midbrain was found in isolated mice between 3 and 6 weeks. These results are discussed in terms of interactions between serotonergic alterations and isolation-induced aggression. © 1998 Elsevier Science Inc.

Social isolation Serotonergic metabolism 5-HT_{1A} receptor 5-HT_{2A} receptor Aggression Mice

ISOLATION-induced behavioral alterations in mice are used to study underlying neurochemical mechanisms. Longitudinal studies from 1 day up to 18 weeks have shown that especially aggressive behavior of individually housed mice was transiently increased reaching a maximum after 3 and 6 weeks (17,24). Several studies emphasize the major role of serotonin (5-hydroxytryptamine; 5-HT) in the control of aggression in rodents and humans (3,25,26,29). In addition, social isolation has been shown to induce decreased cerebral 5-HT metabolism (18,33).

However, little is known about pre- and postsynaptic serotonergic alterations in dependence on the duration of social isolation. There is some evidence for behavioral 5-HT_{2A}/5-HT_{1A} postsynaptic supersensitivity in isolated rats (34). Frances et al. (9) also found enhanced effects of 8-OH-DPAT in isolated mice, which suggests supersensitivity to 5-HT_{1A} agonists. Thus, we measured serotonin metabolism (ratio 5-HIAA/5-HT) in different brain structures, presynaptic 5-HT_{1A} receptors in the midbrain (autoreceptors located in midbrain raphe nuclei), postsynaptic 5-HT_{1A} receptor binding in the hippocampus, and 5-HT_{2A} receptor binding in the cortex during isolation from 1 day up to 18 weeks.

Mice selected according to their running wheel activity have been shown to differ in their response to drug treatment (16,30), in isolation-induced aggression (17), and in behavioral "despair" (15). Based on these observations we assume that high-active mice (HAM) and low-active mice (LAM) differ in serotonergic characteristics and/or in isolation-induced serotonergic alterations.

We aimed at investigating isolation effects on serotonergic pre- and postsynaptic parameters in various brain regions of HAM and LAM.

METHOD

Animals and Housing

The experiments were performed with male NMRI mice (n = 192, 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

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alterations. Mice were differentiated by their running wheel activity (1 h) according to Jähkel et al. (16).

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

Chemicals

[^{3}H]8-OH-DPAT (137 Ci/mmol) and [^{3}H]-ketanserin (62 Ci/mmol) were purchased from Amersham Buchler (Braunschweig, Germany). Other compounds were obtained as follows: bovine serum albumin, 1-heptanesulfonic acid, 5-hydroxyindole-3-acetic acid (5-HIAA), 5-hydroxytryptamine creatinine sulfate (5-HT), mianserin hydrochloride, and polyethylenimine from Sigma Chemical Co. (St. Louis, MO), and $CaCl_2$, citric acid, methanol, Na_2EDTA, and sodium acetate from Merck (Darmstadt, Germany).

In Vitro Binding Studies

Following decapitation, cerebral cortex, hippocampus, and midbrain region were 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 rehomogenized (five strokes) in the same puffer and incubated for 10 min at 37°C to remove endogenous serotonin (22). Membranes were rehomogenized in 50 mM Tris-HCl, 2 mM $CaCl_2$, pH 7.4, after centrifugation. Binding assays were performed using 0.1-ml aliquots (equivalent to 20–25 μg (hippocampus), 25–30 μg (midbrain region), and 60–70 μg (cortex) protein).

Receptor binding assays were performed using [^{3}H]8-OH-DPAT and [^{3}H]-ketanserin as binding ligands for 5-HT_{1A} receptors (hippocampus and midbrain region) and cortical 5-HT_{2A} receptors (10,19).

5-HT_{1A} receptor assay was performed according to Hall et al. (11). Hippocampus and midbrain region membranes were incubated at 23°C for 30 min in a final volume of 0.3 ml 50 mM Tris-HCl, pH 7.4, containing 2 mM $CaCl_2$ and [^{3}H]8-OH-DPAT (0.05–1.6 nM). Nonspecific binding was determined by incubation of samples with 10 μM serotonin. Analyses of both displacement data and linear Scatchard plots ($r > 0.97$) revealed a single high-affinity binding site. In the present study, a single-site model of [^{3}H]8-OH-DPAT binding was most consistent with the data observed, and no evidence was obtained for labeling of other binding sites, for example, 5-HT_7 receptors.

Binding of [^{3}H]-ketanserin (0.2–5 nM) to cortical 5-HT_{2A} receptors was carried out in total incubation volume of 0.3 ml of 50 mM Tris-HCl, 2 mM $CaCl_2$, pH 7.4, in the presence (defining nonspecific binding) and absence of 10 μM mianserin. The binding assay was performed for 60 min at 23°C.

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 a liquid scintillation counter. Analysis of binding data was performed according to Scatchard (31).

Protein content was measured with Bradford's method (5) using bovine serum albumin as the standard.

HPLC Analyses

Decapitated animals' striatum, cortex, hippocampus, as well as cerebellum 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 × 4.6 mm, 3 μm 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_2EDTA. The flow rate was set to 1 ml/min, and the temperature maintained at 31°C. Serotonin and 5-hydroxyindoleacetic acid (5-HIAA) 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 5-HIAA and 1.0 ng/ml for 5-HT. Intra- and interassay variability has been estimated to be 2.8 and 5.7%, 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) 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

Serotonin Metabolism in Different Brain Regions

The basal levels of 5-HT and 5-HIAA of mice on the first day were 932 ± 41 and 570 ± 17 (striatum), 863 ± 36 and 186 ± 13 (cortex), 602 ± 37 and 330 ± 11 (hippocampus), and 226 ± 16 and 126 ± 8 (cerebellum) ng/g wet weight.

The ratio 5-HIAA/5-HT as serotonin metabolism index was generally reduced in the investigated brain regions of isolated HAM and LAM (Fig. 1A–D). However, the course of reduction was different in the brain regions. Whereas reduced serotonin metabolism was observed after short-term isolation (1 week) and 6 weeks (Fig. 1B) in the striatum, cortical serotonin metabolism was transiently reduced after 6 and 12 weeks (Fig. 1A). Reduced hippocampal serotonin metabolism was found after long-term isolation (12 and 18 weeks) (Fig. 1C). Cerebellar serotonin metabolism was reduced in dependence on activity type after 3 and 12 weeks in isolated HAM and after 18 weeks in isolated LAM (Fig. 1D). HAM's serotonin metabolism seems to be more affected by social isolation, especially after 12 weeks in the cortex, hippocampus, and cerebellum and after 6 weeks in the striatum (Fig. 1A–D). However, statistically significant interactions between housing and activity type were not found in these brain structures [cortex: $F(1, 158) = 0.31$, $p = 0.70$; hippocampus: $F(1, 159) = 0.81$, $p = 0.5$; cerebellum: $F(1, 159) = 0.85$, $p = 0.37$; striatum: $F(1, 159) = 1.2$, $p = 0.31$].

5-HT_{2A} Receptors in the Cortex

No significant affinity (K_d) differences between isolated and group-housed mice or between mice of the different activity types were found. However, housing condition has a significant influence on receptor density [B_{max} $F(1, 159) = 6.1$, $p < 0.02$, with significant interaction between housing and activity type, $F(1, 159) = 4.5$, $p < 0.05$]. After 6 and 18 weeks isolated HAM will have increased cortical 5-HT_{2A} binding sites compared to group-housed HAM (Fig. 2). These isolation induced alterations were not found in LAM. Between 1 day

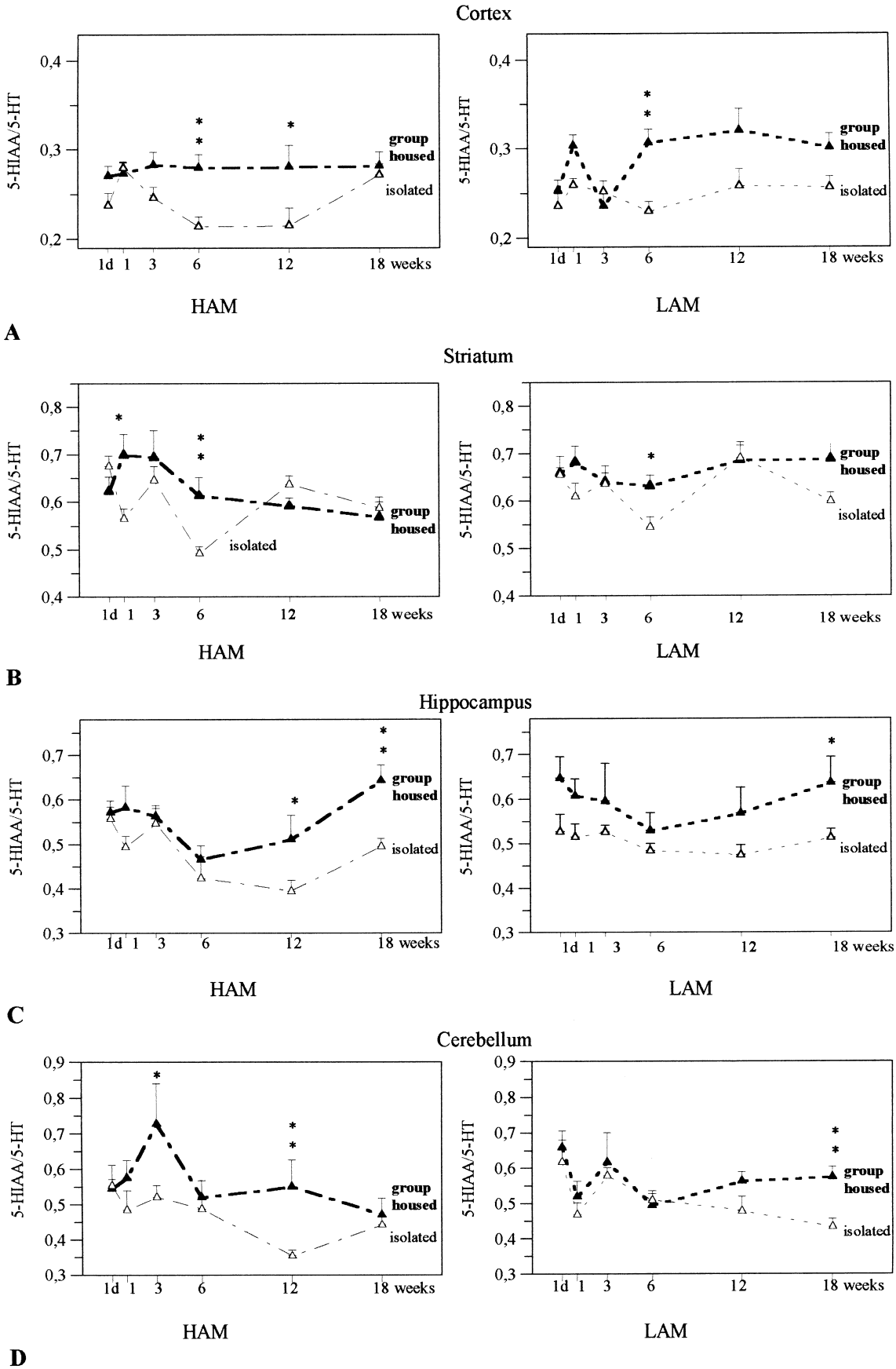

FIG. 1. (A–D) Serotonin metabolism (5-HIAA/5-HT) of group-housed (closed triangles) and isolated (open triangels) HAM and LAM (1 day to 18 weeks) in the cortex (A), striatum (B), hippocampus (C), and cerebellum (D). Error bars indicate SEM ($n = 8$). *$p < 0.05$, *$p < 0.01$.

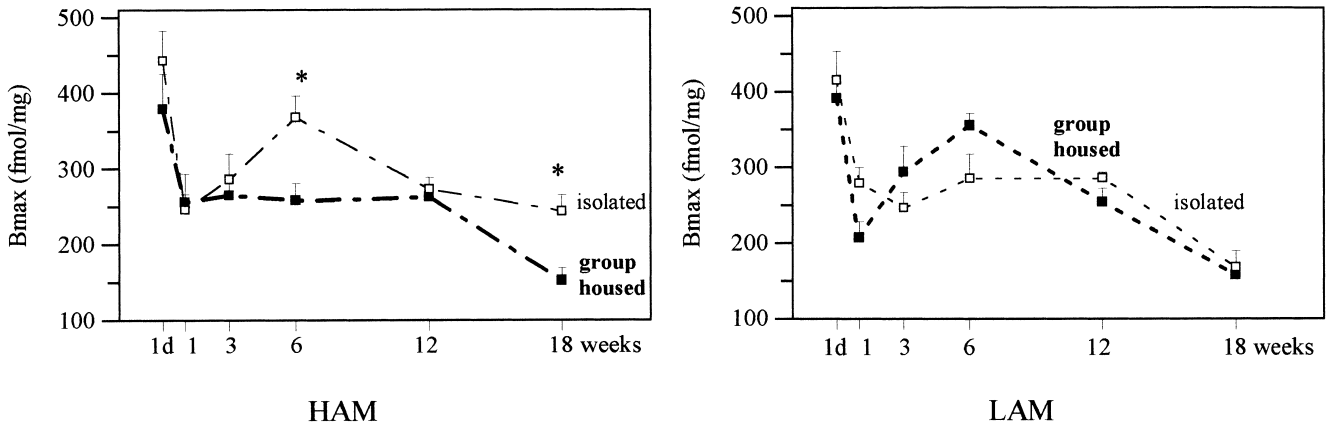

FIG. 2. Receptor density (B_{max}) of cortical 5-HT_{2A} receptors of group-housed (closed squares) and isolated (open squares) HAM and LAM (1 day to 18 weeks). Error bars indicate SEM ($n = 8$). *$p < 0.05$.

and 1 week a sharp decrease of B_{max} values was found in isolated and group-housed mice.

5-HT_{1A} Receptors in the Hippocampus

Housing condition and activity type did not influence hippocampal 5-HT_{1A} receptor density. But there was a significant difference in the affinity (K_d of [^{3}H]8-OH-DPAT to hippocampal 5-HT_{1A} receptors between isolated and group-housed mice, $F(1, 155) = 8.3, p < 0.02$) (Fig. 3). Compared to group-housed mice K_d values of isolated mice were increased (reduced affinity) after short-time isolation lasting up to 3 weeks. Statistically significant differences were not found between HAM and LAM.

5-HT_{1A} Receptors in the Midbrain

Housing condition and activity type did not influence the affinity of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors in the midbrain. However, analysis of variance (ANOVA) revealed a significant effect of housing conditions on the 5-HT_{1A} receptor density in the midbrain, $F(1, 159) = 3.6, p < 0.05$. Isolated mice have reduced B_{max} values after 3 (LAM) and 6 weeks (HAM), as shown in Fig. 4. Despite stronger isolation-induced effects in HAM, differences between HAM and LAM of the same housing conditions were not found. It is particularly remarkable that a generally marked increase of B_{max} values was detected between 1 day and 1 week.

DISCUSSION

As mentioned above, several investigators reported that individually housed mice or rats have a lower serotonin metabolism than group-housed animals. Such effects were found in the rat nucleus accumbens, prefrontal cortex, and hippocampus (4,28,32). In mice, social isolation has been shown to induce a decrease of 5-HT turnover in the entire brain and diencephalon (18,33). There are, however, limited data available on the time course of serotonergic changes in different brain structures. According to Hilakivi et al. (12), isolating the mice for 2, 5, 10, and 20 days did not produce any alterations in central serotonin metabolism. Our present results indicate that individual housing of mice may be associated with lowered serotonin metabolism, depending on isolation time and brain structure.

Whereas a significant transient decrease in the striatum and the cortex was detected after short-term (1 week) and

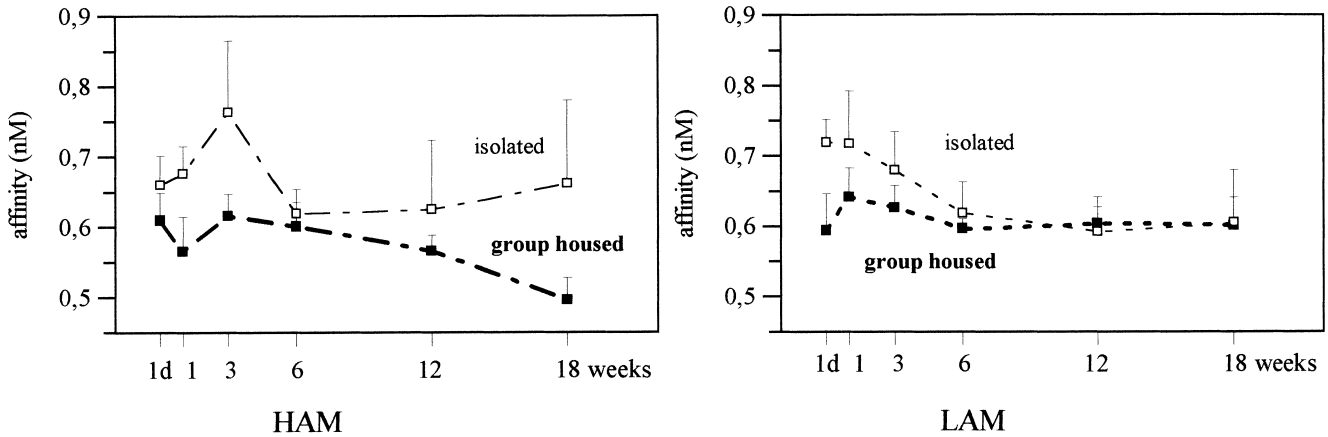

FIG. 3. Affinity of 8-OH-DPAT to hippocampal 5-HT_{1A} receptors of group-housed (closed squares) and isolated (open squares) HAM and LAM (1 day to 18 weeks). Error bars indicate SEM ($n = 8$).

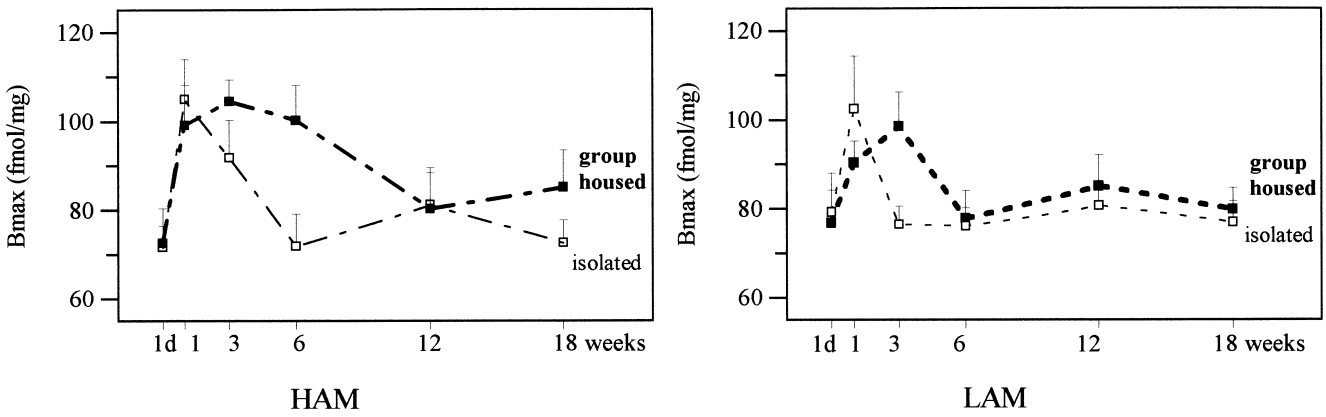

FIG. 4. Receptor density (B_{max}) of presynaptic 5-HT_{1A} receptors in the midbrain of group-housed (closed squares) and isolated (open squares) HAM and LAM (1 day to 18 weeks). Error bars indicate SEM (n = 8).

longer isolation (6–12 weeks), a significant fall of hippocampal and cerebellar serotonin metabolism was found later (12–18 weeks). The specific time course of serotonergic alterations in certain brain structures suggests serotonergic projections to striatum/cortex and hippocampus/cerebellum to be differently influenced by social isolation. Paralleling the transient decrease in the striatum and the cortex, such a transient alteration has been found in isolation-induced aggression (17,24). Thus, a modulatory role of serotonergic systems on aggressive behavior can be postulated, consistent with findings of other laboratories (3,25,26). Furthermore, chronic lithium treatment during social isolation prevents isolation-induced aggression (23). Among others, chronic lithium rises cortical serotonin metabolism (13,20) and thus may counteract isolation-induced fall of cortical serotonin metabolism.

The present investigation has been also designed to assess the impact of endogenous disposition on isolation-induced alterations. We found that striatal and hippocampal serotonin metabolism of high-active mice (HAM) were especially more affected by social isolation. Thus, HAM's serotonergic systems were found to be more reactive to environmental disturbances. Likewise, social isolation mediated upregulation of cortical 5-HT_{2A} receptors after 6 and 18 weeks only in HAM. The increased density of cortical 5-HT_{2A} receptors in individually housed HAM could be due to reduced serotonin metabolism. However, individual disposition seems to be crucial in receptor upregulation, because it could not be measured in LAM. Isolation-induced upregulation of cortical 5-HT_{2A} receptors in HAM corresponds to the reported 5-HT_{2A} postsynaptic receptor supersensitivity of isolated rats (34).

Regarding the time course of receptor alterations, an initial decrease of 5-HT_{2A} receptors was found in isolated and group-housed mice between 1 day and 1 week. This suggests that the initial change of housing condition could be connected with a rapid increase of 5-HT release and receptor downregulation. Interestingly, various types of stress have been found to activate brain 5-HT systems (1,14). Thus, regarding the time course of individual housing, two different phases can be distinguished. First, changed housing condition leads to rapid stress reaction connected with increased serotonin metabolism and cortical receptor 5-HT_{2A} downregulation. After 3 weeks isolation-induced changes with a decrease in serotonin metabolism and an upregulation of cortical 5-HT_{2A} receptors can be detected that may be related to adaptive processes.

Hippocampal serotonin metabolism fell after 12 and 18 isolation weeks, but the density of postsynaptic 5-HT_{1A} receptors in the hippocampus was not different between grouped and isolated mice. In other studies hippocampal 5-HT_{1A} receptor alterations were not found after long-term treatment with 5-HT_{1A} agonists or serotonin uptake inhibitors (2,7,8) either. Different adaptive mechanisms may explain the relative resistance of postsynaptic 5-HT_{1A} receptors to down-/upregulation contrary to their presynaptic counterparts in the midbrain. However, we found significant differences in the affinity of 5-HT_{1A} receptors between grouped and isolated-housed mice in the initial isolation phase. Isolated mice have reduced affinity (increased $K_d$values) between 1 day and 3 weeks with this, probably resulting from receptor modification. Putative sites for PK-C–mediated phosphorylation have been described (27). Given the fact that corticosterone can influence hippocampal 5-HT_{1A} receptor function (6,21), it is conceivable that affinity alterations may be mediated by steroid stress hormones.

Isolation-induced upregulation of presynaptic 5-HT_{1A} receptor density in the midbrain was found after 3 and 6 weeks. These alterations were transient and not measured after long-term isolation (12 and 18 weeks).

Considering the time course of housing-induced alterations, we found reciprocal changes of cortical 5-HT_{2A} receptor density and presynaptic 5-HT_{1A} receptor density in the midbrain region. Whereas cortical 5-HT_{2A} receptors decreased, presynaptic 5-HT_{1A} receptor density increased between 1 day and 1 week. Functional interrelationships between these structures especially in short-term adaptive processes may be present.

However, we have not definitive evidence whether changes in B_{max} are consistent with alterations in receptor density. This open question and the relation between receptor gene expression and receptor density as well as the phenomena of absent relation between changes in serotonergic metabolism and postsynaptic receptor modifications could be elucidated by autoradiographic and in situ hybridization studies. With these techniques we should be able to measure regulations of gene expression and density of other receptor populations (e.g., 5-HT_{2A} levels in the striatum) in response of different housing.

In summary, we found transient alterations of cortical and striatal serotonin metabolism in hippocampal 5-HT_{1A} receptor affinity and density of presynaptic 5-HT_{1A} receptors in the midbrain. Aggressive behavior of isolated mice transiently changes with a maximum increase between 3 and 6 weeks also (17,24). Moreover, stronger isolation-induced serotonergic al-

terations (metabolism and upregulation of cortical 5-HT_2 receptors) were found in HAM. In parallel, behavioral investigations have also shown a more marked aggressivity increase in HAM (15). Therefore, our results correspond to the hypothesis that reduced 5-HT neurotransmission tends to increase aggressive behavior (3,25).

But it must be taken into account that serotonin is not the only neurotransmitter altered by social isolation in rodents (28), and a balance between 5-HT and other transmitters in the brain may be related to the aggressive behavior that occurs. Further investigations are necessary to clarify interactions between different serotonergic systems and other neurotransmitters in the brain and reveal the role these neurotransmitters play in controlling behavioral events following social isolation in different mice's activity types. Such an experimental approach may be useful to elucidate not only the neurochemistry of aggression, but also other isolation-induced behavioral changes.

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