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Genetic variation in vulnerability to the behavioral effects of neonatal hippocampal damage in rats

(strain specificity/Fischer 344 rats/Lewis rats/mesolimbic dopamine system/animal model)

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ABSTRACT **We explored how two independent variables. one genetic (i.e., specific rat strains) and another environmental (i.e., a developmental excitotoxic hippocampal lesion), contribute to phenotypic variation. Sprague–Dawley (SD), Fischer 344 (F344), and Lewis rats underwent two grades of neonatal excitotoxic damage: small and large ventral hippocampal (SVH and LVH) lesions. Locomotion was tested before puberty [postnatal day 35 (P35)] and after puberty (P56) following exposure to a novel environment or administration of amphetamine. The behavioral effects were strain- and lesion-specific. As shown previously, SD rats with LVH lesions displayed enhanced spontaneous and amphetamine-induced locomotion as compared with controls at P56, but not at P35. SVH lesions in SD rats had no effect at any age. In F344 rats with LVH lesions, enhanced spontaneous and amphetamine-induced locomotion appeared early (P35) and was exaggerated at P56. SVH lesions in F344 rats resulted in a pattern of effects analogous to LVH lesions in SD rats—i.e., postpubertal onset of hyperlocomotion (P56). In Lewis rats, LVH lesions had no significant effect on novelty- or amphetamine-induced locomotion at any age. These data show that the degree of genetic predisposition and the extent of early induced hippocampal defect contribute to the particular pattern of behavioral outcome. These results may have implications for modeling interactions of genetic and environmental factors involved in schizophrenia, a disorder characterized by phenotypic heterogeneity, genetic predisposition, a developmental hippocampal abnormality, and vulnerability to environmental stress.**

Genetic factors that affect brain function can be studied in genetically inbred animal strains. For instance, three strains of rats—Sprague–Dawley (SD), Lewis, and Fischer 344 (F344)—differ substantially in a number of respects, including responsiveness to stress, predisposition to inflammatory diseases, and preference for drugs of abuse (1–5). Moreover, it has been suggested that these differences are associated with differential responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis to stressful or inflammatory stimuli (3, 6, 7), differential interactions between neurotransmitter systems and the HPA axis (8), and the functional state of the mesolimbic dopamine (DA) system (9–12). F344 and Lewis rats appear to represent two ends of a spectrum of stress responsivity; F344 rats are hyperresponsive to stress whereas Lewis rats are hyporesponsive to stress as assessed by behavioral and neuroendocrine responses to an open field, swim test, restraint, etc. Outbred SD rats exhibit an intermediate response to stress compared with these two inbred strains. Thus, comparisons of these rat strains may provide insights into how genetic factors influence stress-related behaviors.

We have demonstrated that SD rats with neonatally induced excitotoxic lesions of the ventral hippocampal formation exhibit a variety of abnormal behaviors, including enhanced locomotor hyperresponsiveness to stress, accentuated motoric changes in response to DA agonists and antagonists, and deficits in sensorimotor gating (13–15). These lesion-induced behavioral disturbances in SD rats are detectable only after puberty and are thought to be linked to excessive DA activity in the mesolimbic/nigrostriatal systems (16, 17). Moreover, there is evidence suggesting that the severity of behavioral changes may be related to the extent of hippocampal damage.

In the present study we sought to determine how these two factors, one genetic (represented by three strains of rats) and one environmental (represented by variations in the extent of neonatal hippocampal damage), affect patterns of behavioral changes related to DA function. Because stress appears to play a role in modulating the effects of these lesions, we anticipated that in animals with genetically determined hyperresponsiveness to stress—i.e., in F344 rats—the effects of the lesion would be exaggerated and, conversely, in rats that show relative resistance to stress—i.e., in Lewis rats—these effects would be attenuated. We assumed that SD rats would exhibit an intermediate response. By infusing varying amounts of the neurotoxin ibotenic acid, we intended to vary the extent of the VH lesion and thus alter the severity of behavioral deficits within strains. The experimental method chosen for phenotypic evaluation was novelty- and amphetamine-induced hyperlocomotion tested before and after puberty in computerized photocell-equipped cages.

MATERIALS AND METHODS

Surgery. Rat pups were lesioned as described (13). Pregnant SD (Zivic–Miller), F344 (Charles River Breeding Laboratories), and Lewis (Charles River Breeding Laboratories) rats obtained at 12–15 days of gestation were housed individually in breeding cages with a 12-hr light/12-hr dark cycle and fed ad libitum. On postnatal day 7 (P7), the pups (weight: 15–18 g for SD, 9–13 g for F344, and 12–16 g for Lewis) were anesthetized by hypothermia (placed on ice for 10–20 min). An incision was made in the skin overlying the skull and 0.3 μl [for large ventral hippocampal (LVH) lesions] or 0.15 μl [for small ventral hippocampal (SVH) lesions] of ibotenic acid solution (Sigma; 10 μg/μl) or artificial cerebrospinal fluid (in sham-operated rats) was infused bilaterally into the ventral hippocampal formation at 0.15 μl/min. The injection site was intended to be identical in all three strains: for SD rats, AP −3.0 mm, ML ±3.5 mm, VD −5.0 mm; for F344 rats, AP −2.2 mm, ML ±3.0 mm, VD −4.5 mm; and for Lewis rats, AP −2.3 mm, ML ±3.1 mm, VD −4.5 mm (relative to bregma). The pups were warmed and then returned to their mothers. On P25, animals were weaned and separated according to lesion.

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Abbreviations: SD, Sprague–Dawley; F344, Fischer 344; P*n*, postnatal day *n*; SVH, small ventral hippocampal; LVH, large ventral hippocampal; HPA, hypothalamic–pituitary–adrenal; DA, dopamine.

Behavioral Testing. Rats were lesioned and tested during three consecutive weeks, each strain separately every day over 1 week. The same rats were tested at P35 and P56. In addition, a cohort of F344 rats with sham and ibotenic acid lesions was tested only at P56 to control for a possible effect of sensitization due to prior exposure to amphetamine. Because no such effect was detected (i.e., novelty- or amphetamine-induced locomotion of rats tested only at P56 did not significantly differ from that tested at P35 and P56), these data were pooled for a final overall analysis of locomotion. Numbers of animals tested were 42 SD rats, 67 F344 rats (of which 44 were tested twice, and 23 only on P56), and 52 Lewis rats (total $n = 161$). On the day of testing, animals were transferred from their home cages to the testing area and weighed. Rats were then placed in clear Plexiglas photocell activity monitors (42 cm × 42 cm × 30 cm) [Omnitech (Columbus, OH) model RXYZCM 16], and total distance traveled (cm) was measured during 1 hr. Rats then received 0.9% NaCl injections (1 ml/kg) and were monitored for another hour. Finally, (*S*)-amphetamine sulfate (RBI) was administered (1.5 mg/kg, i.p.) and locomotion was measured for 1.5 hr.

After completion of behavioral testing, the brains of rats were quickly removed, frozen, sectioned, and thionin-stained. The extent of the lesion, defined as the area of neuronal loss and/or cavitation, was characterized by light microscopy.

Data Analysis. Because for Lewis rats only two lesioned groups (sham and LVH) were included in the analysis (see *Results*), SVH and LVH groups were combined across strains for an overall statistical analysis of the data. Moreover, because some rats were tested only at P56, the age variable was considered an independent factor. Thus, the data were analyzed by a four-way ANOVA with lesion status (sham and lesion), strain (SD, F344, and Lewis), and age (P35 and P56) as independent factors, testing condition (novelty and amphetamine) as a repeated measure, and locomotion as a dependent variable. Fisher probable least-squares difference (PLSD) post-hoc tests were performed when the main effects were significant. In post-hoc comparisons, all three lesion groups were included (sham, SVH, and LVH).

RESULTS

Verification of the Lesion. Thionin-stained 20-μm brain sections of the lesioned rats were examined by low-power light microscopy. From the area of neuronal loss and/or cavitation within the boundaries of the ventral hippocampal formation, the brains were assigned to either a LVH or a SVH lesion group. The LVH lesion was characterized by neuronal loss throughout all cytoarchitectural subdivisions (CA1–CA3), including parts of the dentate gyrus and subiculum, in the temporal portions of the hippocampal formation [plates 34–41, according to the atlas of Paxinos and Watson (18)] (Fig. 1). Moreover, in all brains with LVH lesions, a large area of cavitation was observed in the vicinity of the injection site. The LVH lesion corresponds to that previously described by us in SD rats (13). The SVH lesion was much more restricted and resulted in neuronal loss at the site of injection, but not in cavitation. The primary area of neuronal loss included CA1 and CA2 subregions (Fig. 2). No damage was seen in the dentate gyrus or subiculum.

Due to extrahippocampal damage, 3, 4, and 4 rats were deleted from further analysis from SD, F344, and Lewis groups, respectively. All remaining SD rats that were infused with 3 μg (0.3 μl) of ibotenic acid were assigned to the LVH lesion group ($n = 16$), and those that were infused with 1.5 μg (0.15 μl) were assigned to the SVH group ($n = 10$). Again, as in SD rats, all remaining F344 rats that received 3 μg (0.3 μl) of ibotenic acid had, according to the criteria outlined above, LVH lesions ($n = 11$), and those that received 1.5 μg (0.15 μl) had SVH lesions ($n = 21$). In the Lewis group, although in the remaining animals which received 3 μg (0.3 μl) of ibotenic acid ($n = 13$) the lesion was confined to the hippocampal formation, it destroyed almost the whole hippocampus, including subregions CA1–CA3 in the dorsal portion. The only part spared was the most dorsal aspect of the dentate gyrus. Because this lesion greatly exceeded damage in SD and F344 rats, and thus was not comparable to the lesions in these strains, Lewis rats with total hippocampal lesions were not included in the analysis of behavioral data. Lewis rats that were infused with 1.5 μg (0.15 μl) of ibotenic acid showed destruction similar to that obtained with 3 μg (0.3 μl) in SD and F344 rats and thus were assigned to the LVH group ($n = 14$).

Behavioral Testing. Locomotor activity varied depending on the specific strain, on the characteristics of the lesion, on the age of the animals, and on the testing condition. ANOVA showed significant main effects of strain ($F_{2,498} = 50.8$, $P < 0.0001$), age ($F_{1,498} = 30.2$, $P < 0.0001$), lesion ($F_{1,498} = 30.1$,

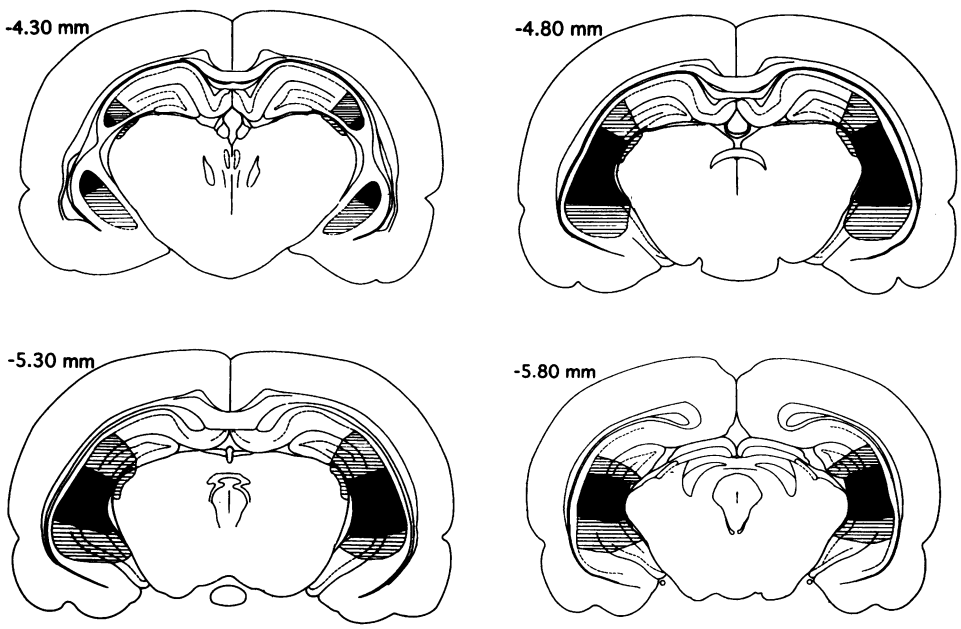

FIG. 1. Lesion boundaries defined as the area of neuronal absence and determined from thionin-stained coronal sections from rats with LVH lesions. Coordinates refer to distance (mm) posterior to bregma. Black and striped areas indicate the smallest and largest lesions, respectively.

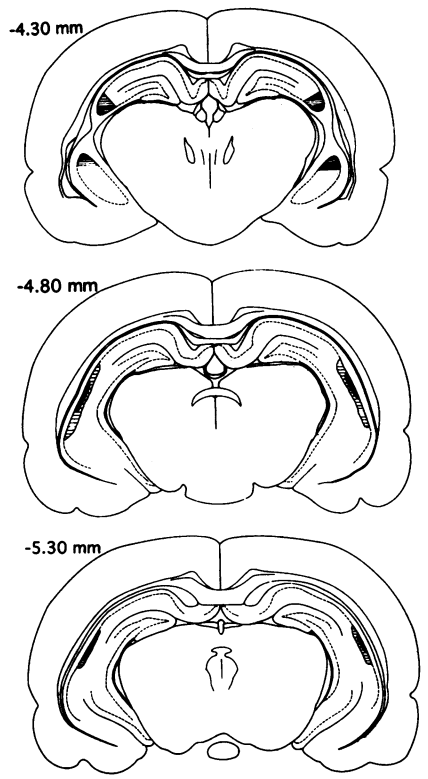

FIG. 2. Lesion boundaries determined in rats with SVH lesions. For details, see Fig. 1.

$P < 0.0001$), and testing condition ($F_{1,498} = 859.7, P < 0.0001$). These effects were influenced by one another as indicated by several significant interactions, including an interaction between strain and lesion ($F_{2,498} = 7.4, P < 0.001$), between strain and testing condition ($F_{2,498} = 56.2, P < 0.0001$), between age and testing condition ($F_{1,498} = 24.5, P < 0.0001$), among strain, age, and testing condition ($F_{1,498} = 3.0, P < 0.05$), between lesion and testing condition ($F_{1,498} = 23.9, P < 0.0001$), and among strain, lesion, and testing condition ($F_{1,498} = 6.2, P < 0.01$). There was a trend toward a significant strain-by-age interaction ($F_{2,498} = 2.5, P = 0.08$). All other interactions, including the interaction among all four factors (strain by age by lesion by testing condition), were not significant.

Post-hoc comparisons showed that sham-operated rats of all three strains displayed similar spontaneous locomotor activity after exposure to a novel environment (Figs. 3 and 4). Moreover, the level of spontaneous activity did not considerably change with age. Amphetamine-induced locomotion, however, differed dramatically across the strains at P35, and for each strain consistently increased from P35 to P56. At P35, SD rats displayed the lowest level of amphetamine-induced locomotion (5368 ± 786 cm), F344 rats were significantly more active (11,096 ± 1412 cm), and Lewis rats showed the highest level of amphetamine-induced locomotor stimulation (16,494 ± 1278 cm, $P < 0.05$; Fig. 3). At P56, however, SD controls did not significantly differ from F344 sham-operated rats (9945 ± 1292 cm vs. 13,091 ± 791 cm, respectively; not significant). Lewis rats still displayed significantly greater amphetamine-induced locomotion than SD or F344 rats (24,450 ± 1289 cm, $P < 0.05$; Fig. 4).

Further post-hoc analysis revealed that within each strain, the lesions (SVH and LVH) resulted in different behavioral patterns when compared with the corresponding sham-operated group.

SD Rats. At P35 there were no significant effects of either SVH or LVH lesion on locomotor activity displayed in a novel environment or after amphetamine (Fig. 3). The SVH-lesion

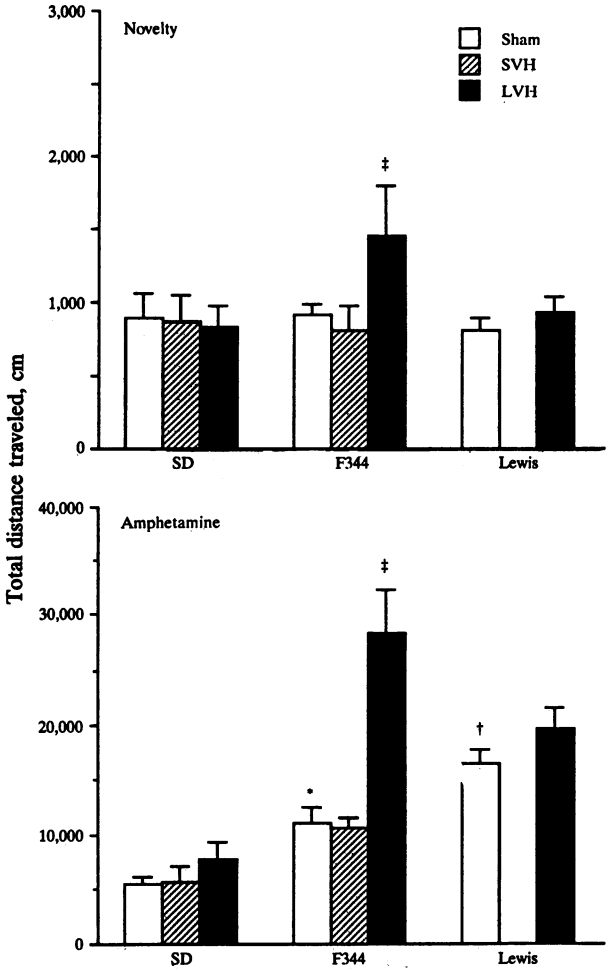

FIG. 3. Locomotor activity measured on P35 in rats with neonatal (P7) control (Sham), SVH, and LVH lesions. *, Significantly different from sham-operated SD group ($P < 0.05$); †, significantly different from sham SD and sham F344 groups ($P < 0.05$); ‡, significantly different from sham and SVH groups of the same strain ($P < 0.05$).

animals also did not differ from sham-operated controls at P56. However, rats with LVH lesions were significantly more active at P56 after exposure to novelty ($P < 0.05$) and after amphetamine ($P < 0.05$) than either the SVH or the sham-operated group (Fig. 4). This finding of delayed emergence of hyperactivity in rats with LVH lesions is in accord with our previous data (13).

F344 Rats. At P35, rats with SVH lesions did not significantly differ from sham-operated controls after exposure to novelty or amphetamine (Fig. 3). At P56, however, SVH-lesion animals expressed increased locomotor activity in response to both novelty ($P < 0.05$) and amphetamine ($P < 0.05$) as compared with controls (Fig. 4). The pattern of abnormalities characterized by delayed emergence of hyperlocomotion resembles that observed in SD rats with LVH lesions. F344 animals with LVH lesions showed increased activity in a novel environment and after amphetamine at both ages as compared with controls ($P < 0.05$). They were also more active than animals with SVH lesions in both testing conditions at P35, as well as after amphetamine administration at P56 ($P < 0.05$). Thus, LVH lesions in F344 rats resulted in an early appearance of hyperactivity, which was further potentiated at an older age.

Lewis Rats. Lewis rats with LVH lesions did not differ from sham-operated controls in total distance traveled in the novel environment or after amphetamine administration at any age tested (Figs. 3 and 4). Lewis rats seemed thus resistant to the behavioral effects of this lesion. However, sham-operated

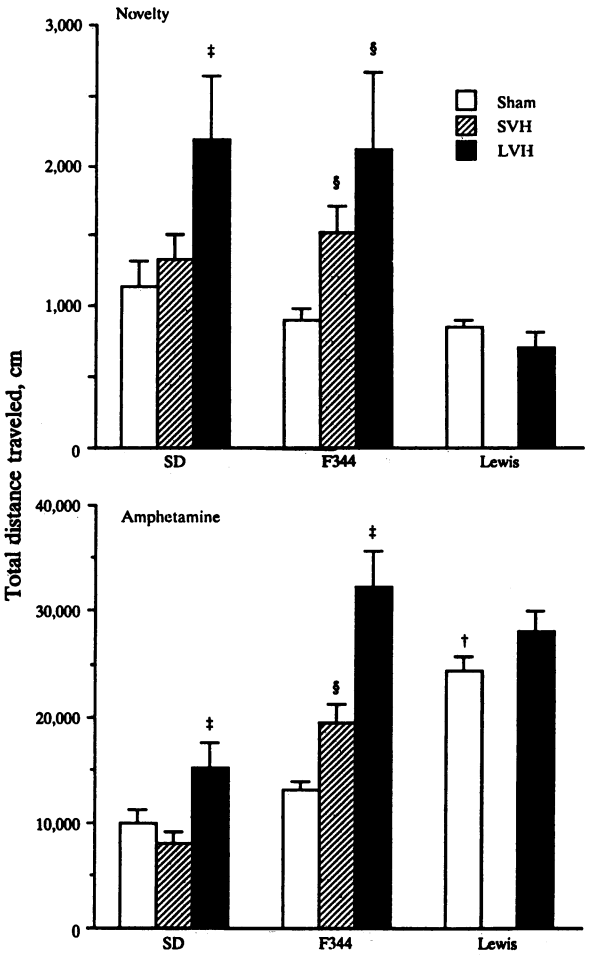

FIG. 4. Locomotor activity measured on P56. For details, see Fig. 3. †, Significantly different from sham SD and sham F344 groups ($P < 0.05$); ‡, significantly different from sham and SVH groups of the same strain ($P < 0.05$); §, significantly different from sham group of the same strain ($P < 0.05$).

Lewis rats exhibited the highest level of amphetamine-induced locomotion compared with other strains, suggesting that the effect of the lesion on amphetamine-induced locomotion might not be detectable in this strain due to a "ceiling" effect. Further evaluation of the data revealed, however, that at P56 Lewis rats with almost total hippocampal lesions, which were not included in the comparisons, showed considerably more amphetamine-induced locomotor activity than Lewis rats with LVH lesions or sham-operated animals (47,116 ± 6015 cm vs. 28,222 ± 1789 cm vs. 24,450 ± 1289 cm, respectively). This indicated that, at least under certain circumstances, Lewis rats were physically capable of traveling a greater distance.

DISCUSSION

The results demonstrate that SD, F344, and Lewis rats display different vulnerability to the behavioral effects of neurodevelopmental excitotoxic hippocampal damage. Further, the lesion-induced behavioral effects, in terms of both the severity of behavioral disturbances and the time at which they appear, depend on the extent of damage. In other words, both factors—one genetic and one environmental—contribute to a particular phenotype associated with neonatal hippocampal damage.

Strain specificity in responsiveness of these rats to other environmental factors has previously been demonstrated. For instance, Lewis, F344, and SD rats differ considerably in their susceptibility to a number of autoimmune diseases (19, 20) and in their neuroendocrine and behavioral responsiveness to stress (4). In addition, there may be a causative relationship between these two phenomena (21). Lewis rats, which are particularly susceptible to inflammatory diseases, appear to be deficient in their ability to respond to a variety of stressful stimuli. In response to stress mediators, their activation of the HPA axis, including the synthesis and secretion of hypothalamic corticotropin-releasing factor and plasma corticotropin and corticosterone, appears to be inadequate as compared with other strains (4, 21–23). Lewis rats also show blunted behavioral responses to emotional and physical stressors, such as less grooming and locomotion in the inner versus outer areas of an open field (3). Conversely, F344 rats, which are relatively resistant to inflammatory diseases, exhibit potentiated corticotropin-releasing factor, corticotropin, and corticosterone responses to stressful stimuli (24). F344 rats are considered "hyperexcitable and difficult to handle" and "more sensitive to external stimuli and highly emotional" (25), as well as "extremely fearful" and "less able to habituate or adapt to repeated stress" (24) when compared with SD or Lewis rats. SD rats, on the other hand, exhibit moderate susceptibility to inflammation and moderate responsiveness to stress when compared with either Lewis or F344 rats. Rats of these three strains differ also in their preference for drugs of abuse such as ethanol, cocaine, morphine, and tetrahydrocannabinol. Lewis rats show much higher rates of self-administration of opiates, alcohol, and cocaine and greater intracranial self-stimulation responses to cannabinoids than the two other strains (12, 26, 27).

In attempts to explain these strain-related differences, numerous neurochemical studies have been undertaken. The results indicate that there are, indeed, major differences in the function of DA and serotonin systems between Lewis, SD, and F344 rats. For example, F344 and Lewis rats express different levels of tyrosine hydroxylase exclusively in brain areas implicated in mediating the reinforcing properties of drugs of abuse (10, 12)—i.e., the mesolimbic but not the nigrostriatal DA pathways (28–30). Despite a lack of differences in basal levels of DA, Lewis rats manifest profound increases in cannabinoid-induced extracellular DA overflow in the nucleus accumbens, as measured by *in vivo* microdialysis, compared with SD rats (9). Lewis rats also express lower levels of frontal cortical and hippocampal 5-HT1A serotonin receptor mRNA and show reduced density of 5-HT1A binding sites in comparison with SD or F344 rats (31). These differences, whether primary or secondary to the differential responsiveness of the HPA axis, may play a role in augmenting phenotypic responses to stress (31). Interestingly, no differences were detected in the expression or binding properties of D2 DA receptors between these three strains (32).

While these data suggest neurochemical differences that might account for the diversity of behavioral responsiveness of these genetically different strains of rats to the aforementioned external stimuli, it is difficult to predict which of these differences, if any, might play a role in the differential response of these rats to neonatal hippocampal damage. Nevertheless, the fact that SD, F344, and Lewis rats show differences in functional characteristics of the mesolimbic DA system and responsiveness to stress seems of particular interest.

As we have previously suggested, the constellation of behavioral phenomena associated with the neurodevelopmental lesion of the ventral hippocampus in SD rats, which corresponds to the LVH lesion in this study, is primarily indicative of a hyperfunctional mesolimbic DA system. The possibility of increased DA tone in rats with the neonatal hippocampal lesion is further supported by the ability of the antipsychotic drugs haloperidol and clozapine to block excessive locomotion in these rats (33). Stress is also known to engage DA systems by increasing the metabolic activation of the dopaminergic innervation in the medial prefrontal cortex, nucleus accumbens, and striatum (34, 35).

In accord with our hypothesis that stress exaggerates the effects of this developmental lesion, we now report that F344, the

genetically inbred strain characterized by behavioral and neuroendocrine hyperexcitability to stress, shows uniquely high vulnerability to certain effects of neonatal hippocampal damage. Conversely, Lewis rats, which manifest relative hyporesponsiveness to stressful stimuli, seem to be relatively resistant to the behavioral consequences of the hippocampal lesion. What are the mechanisms by which the lesion-induced effects are either potentiated or attenuated in these different strains of rats? Although there are no data to directly support this, it is tempting to speculate that the genetic variation in sensitivity of the DA system might play a role in modulating the effects of the lesion and that it might be related to the variation in vulnerability to stress. F344 rats would then be predicted to be more sensitive, in this respect, than Lewis rats, and SD rats would display a moderate response. From the current data, it is impossible to elucidate the genetic mechanisms underlying the diverse responses to the neonatal ventral hippocampal damage. Our results demonstrate only that such genetic diversity exists and that it may have profound consequences for the severity of the lesion-induced impairments. This approach may represent a step toward a quantitative trait loci (QTL) analysis of stress vulnerability—i.e., a genetic paradigm used for identifying the chromosomal locations of multiple genes which contribute to quantitative variations in a phenotype (36, 37).

Quite surprisingly, Lewis rats, although hyporesponsive to stress, are the ones significantly more affected by the mesolimbic DA-releasing properties of the cannabinoids (9). It may be assumed that they would be similarly, as compared to the two other strains, affected by amphetamine. In fact, the heightened locomotor activity of the sham-operated Lewis rats in response to amphetamine in our study may support such an assumption. Our results indicate, however, that the basal responsiveness to amphetamine is not a good predictor of the lesion-induced altered response to either amphetamine or novelty. Our data also indicate that the relative vulnerability to the neurotoxic effects of ibotenic acid is not such a predictor either. Lewis rats, which appear to be hypersensitive to the locomotor effects of amphetamine and which also appear hypersensitive to the neurotoxic effects of ibotenic acid, are the least behaviorally affected by ventral hippocampal damage. This apparent paradox underscores that lesion size *per se* is not the critical factor in the strain differences in behavioral effects of the lesion.

We have investigated the effects of this neurodevelopmental lesion in rats as a model of some aspects of schizophrenia, a human disorder characterized by many analogous phenomena, including a developmental structural hippocampal abnormality, postpubertal onset of the diagnostic phenotype, dysregulation of limbic dopaminergic activity, frontal cortical dysfunction, deficits in sensorimotor gating, and vulnerability to stress (38, 39). The extension of our model to include genetically determined factors that bear on stress responsivity and that interact with the behavioral effects of environmental injury broadens the scope of this model in two directions: (*i*) it may now explain additional clinical phenomena associated with schizophrenia, in particular, variations across individuals in apparent genetic loading, in severity of symptoms, and in age of onset; and (*ii*) it models important aspects of the genetic data about schizophrenia that genes appear to convey susceptibility to illness and possibly a latent trait (40).

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