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Sodium Arsanilate-Induced Vestibular Dysfunction in Rats: Effects on Open-Field Behavior and Spontaneous Activity in the Automated Digiscan Monitoring System

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OSSENKOPP, K.-P., A. PRKACIN AND E. L. HARGREAVES. *Sodium arsanilate-induced vestibular dysfunction in rats: Effects on open-field behavior and spontaneous activity in the automated Digiscan monitoring system.* PHARMACOL BIOCHEM BEHAV **36**(4) 875–881, 1990.—Vestibular dysfunction was chemically induced in Long-Evans rats by intratympanic injections (30 mg per side) of sodium arsanilate (atoxyl). Following a one-week recovery period the rats were behaviorally assayed for integrity of the labyrinthine systems. All subjects were tested for presence of the air-righting reflex, the contact-righting reflex (by lightly holding a sheet of Plexiglas against the soles of the rat's feet), and body rotation-induced nystagmus. All animals were then tested for their ability to remain on a small (15 × 15 cm) platform. Next, the subjects were given two 10-min open-field tests during which ambulation, rearing, grooming, and defecation responses were recorded. Four to five weeks later all rats were tested twice (60 min per session) in the automated Digiscan Activity Monitor which provides a multivariate assessment of spontaneous motor activity. The rats with vestibular dysfunction (Group VNX) took significantly less time to fall off the platform ($p<0.01$). They also exhibited significantly more open-field ambulation but fewer rearing responses ($ps<0.01$). An examination of group correlation coefficients for open-field variables and the platform test scores revealed some interesting group differences ($ps<0.05$). In the Digiscan tests the atoxyl-treated rats exhibited fewer number of horizontal movements, but increased speed for these movements ($ps<0.05$). Vertical movements did not differ significantly in incidence, but these movements were greatly reduced in duration ($p<0.001$). In general, changes in spontaneous behavior observed in the sodium arsanilate-treated rats were consistent with a loss in ability to balance on the two hind feet (during rearing or grooming) and a redirecting of exploratory vertical movement sequences toward horizontal locomotion, especially in the open-field test. The multivariate behavioral assessment available in the Digiscan Activity Monitoring system seems to be especially useful in the examination of behavioral components affected by vestibular dysfunction.

Vestibular system Sodium arsanilate Open-field behavior Locomotor behavior Labyrinthectomy
Digiscan monitoring system Multivariate assessment Rats

THE vestibular apparatus is a structure common to vertebrates from fish to birds and mammals. It evolved to provide information not only about body and/or head movement and orientation in animals, but also to support movement in relation to gravity. This system detects the position and motion of the head in space and, together with information from visual, proprioceptive, and other somatosensory receptors, provides a multimodal integrated system that the organism can then use for spatial orientation (23). Although mammals can maintain body orientation when one of these inputs is absent, it has been found that vestibular dysfunction can have pronounced and long-lasting effects on behavior.

Vestibular function in rats has been investigated in several studies which have examined body rotation about a vertical axis as an aversive (3, 7, 15, 16) or stress-inducing (4,18) stimulus and the contribution of vestibular input to spatial orientation (12, 14, 17, 24). Previous studies have demonstrated ototoxic effects of a variety of substances in pigeons, mice, pigs, dogs and man (2, 8, 13). As well, several studies have now shown that rats can be chemically labyrinthectomized with sodium arsanilate. This com-

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pound is an arsenic derivative (13) and intratympanic injections of sodium arsanilate (or atoxyl) have been shown to result in vestibular nerve degeneration in the brainstem (1,5) with concomitant loss of labyrinthine righting and reduced postural support with exaggerated head dorsiflexion (9, 10, 30). This compound is also thought to be damaging to the secretory cells of the cristae and maculae, eventually disrupting system osmolality and destroying the hair cells (1, 2, 8).

The present study examined the effects of labyrinth dysfunction, induced with atoxyl injections, on spontaneous behavior in an open-field test and then, in a more detailed fashion, with a multivariate examination of behavior in the automated Digiscan Activity Monitor (19, 27, 28). It was felt that, since previous studies [e.g., (10)] had examined the effects of vestibular dysfunction on locomotor activity in a qualitative fashion, a quantitative assessment of changes in locomotor activity would be useful in interpretation of the effects of labyrinthectomy on other behavioral tasks, especially any type of learning task [e.g., (12,17)]. Many performance measures contain a large locomotor component.

Such a rat model with vestibular dysfunction could also prove useful in delineating the more subtle effects of loss of labyrinthine function on behavior in general, and could prove useful in examination of long-term behavioral changes following loss of one or both of the vestibular inputs, and when other sensory inputs are altered or removed.

METHOD

Subjects

Nineteen adult male hooded rats (Long-Evans strain, Charles River, Quebec), weighing between 450 and 650 g, were individually housed in stainless steel wire mesh cages and kept in a colony room at 22±1°C on a 12-hr light:12-hr dark cycle with lights on from 0700 to 1900 hr. The animals were maintained on ad lib food (Purina lab pellets) and water.

Apparatus

Open-field. The open-field was circular, with a diameter of 90 cm, and was enclosed by a wall 30 cm high. The floor and wall of the open-field were black and the floor was divided into 25 equal area sections by thin white lines. The floor was covered with a transparent plastic coating. The open-field apparatus was located inside a large wooden frame which was surrounded on all sides by black curtains. The field was illuminated by two 60-W fluorescent lights located 100 cm above the floor.

Digiscan Activity Monitors. The automated activity monitoring system consisted of 4 Digiscan Animal Activity Monitors (Omnitech Model RXYZCM-16). The monitors consisted of clear Plexiglas boxes measuring 40×40×30.5 cm with infrared monitoring sensors mounted every 2.54 cm along the perimeter (16 infrared beams along each side) and 4.5 cm above the floor. An additional 16 sensors were located 15 cm above the floor of the boxes. Data were collected and analyzed by a Digiscan Analyzer (Omnitech Model DCM) which in turn transmitted the data to an Apple II+ computer with disk drive, where it was stored.

Chemical Labyrinthectomy

Sodium arsanilate (atoxyl), an ototoxic compound (13), was injected intratympanically following the procedure of Horn *et al.* (9). The rats were anesthetized with sodium pentobarbital (Somnotol, 65 mg/kg, IP). Eleven rats (Group VNX) received bilateral intratympanic 0.10 ml of sodium arsanilate solution (300 mg/ml in isotonic saline). The injection needle was inserted through the tympanic membrane until resistance by the auditory ossicles was encountered, then the solution was injected within 3 to 4 sec. Following each injection the ear canal was tightly packed with gelfoam. An additional 8 rats received bilateral intratympanic injections of 0.10 ml isotonic saline (Group SHA). The animals were monitored until the anesthesia had worn off and were then placed back in their home cages to recover.

Testing Procedures

Tests for labyrinth integrity. Following a 1-week recovery period the rats were tested for integrity of vestibular function. The first test examined the ability of the rats to right themselves in the air (air-righting reflex) when held supine and dropped from a height of approximately 45 cm onto a soft surface. A normal rat rights itself in the air, while falling, and lands on its feet. A rat with labyrinth dysfunction will tend to land on its back or side when tested in this manner. A second test (contact righting) examined the behavior of rats when placed supine on a horizontal surface and another horizontal surface (a sheet of Plexiglas) was lightly placed in contact with the soles of the supine animal's feet. Normal rats will right themselves in this test, whereas rats with vestibular dysfunction will lie supine, with their backs in contact with lower surface and their feet in contact with the ventral surface (Plexiglas sheet), and will not right themselves. Labyrinthectomized rats will "step" or "walk" with respect to the ventral surface, as long as at least the hind feet are in contact with the Plexiglas sheet [cf. (30)]. If the Plexiglas surface is removed from contact with all 4 feet, then the labyrinthectomized rats will show a righting response. Finally, all rats were tested for induction of rotation-induced nystagmus following several minutes of body rotation about a vertical axis [see apparatus in (18)] at 70 rpm.

Elevated platform test. All rats were placed on a 15×15 cm platform made of stainless steel wire mesh and located 45 cm above a table top. The animals were then timed for latency to fall off the platform onto the table top. A minimum latency of 3 sec and a maximum value of 180 sec was used to score all trials

Open-field test. Two 10-min open-field tests were administered in the late afternoon to each animal, with 2 to 4 days separating each test session. At the start of each session the rat was placed in one of the peripheral sections of the open-field and the animal's behavior was monitored by an observer for 10 consecutive minutes. The following variables were recorded for each 2-minute segment of the test session: 1) ambulation—the number of open-field sections entered by the subject; 2) rearing responses—the number of times the animal raised both forefeet off the floor and extended its body; 3) defecation—the number of fecal boli deposited in the open-field; 4) grooming—the number of grooming bouts exhibited by the rat. At the end of each session the rat was returned to its home cage and the floor of the open-field was cleaned and sponged over with a weak vinegar solution to remove any residual odors.

Digiscan Activity Monitor test. Four to five weeks after the last open-field test all animals were individually tested for spontaneous levels of locomotor activity. The rats were tested for 1 hr in the late afternoon on each of two days 48 hr apart. The test apparatus was subjected to normal room light levels during all test sessions. The Digiscan Analyzer collected data for each rat and cumulated this data into three 20-min time bins for each test session. The system-differentiated behavioral variables recorded for each test session were: 1) horizontal activity (HA)—total number of beam interruptions for the lower set of infrared beams; 2) movement time (MT)—the amount of time the animal was in motion during a given time sample; 3) total distance (TD)—the horizontal distance travelled by an animal in a given sample period; 4) number of horizontal movements (NHM)—number of

TABLE 1

RESULTS OF THE TESTS FOR LABYRINTH INTEGRITY AND THE ELEVATED PLATFORM TEST

Test	Groups VNX (n=11)	SHA (n=8)
Air-righting reflex	0/11[a]	8/8
Contact-righting reflex	0/11	8/8
Rotation-induced nystagmus	0/11	8/8
Elevated Platform		
Mean latency	36.64	129.13*
S.E.M.	21.22	70.43
Number of Ss with maximum latency	0/11	5/8

[a]Number of subjects in each group that successfully completed the test.
*$p<0.01$.

separate horizontal movements executed by the rat with a minimum stop time of 1 sec to separate movements; 5) average distance (AD)—mean distance travelled per horizontal movement (TD/NHM); 6) average speed (AS)—mean distance travelled per unit time (TD/MT); 7) vertical activity (VA)—total number of beam interruptions for the upper set of beams; 8) vertical time (VT)—the amount of time the animal activated the upper set of beams; 9) number of vertical movements (NVM)—number of separate vertical movements (rearing) separated by at least 1 sec; 10) average time per vertical movement (ATVM)—mean time taken for each vertical movement (VT/NVM).

Data Analysis

The data were analyzed with a mixed design repeated measures analysis of variance and post hoc comparisons used Tukey's HSD procedure [see (22)]. For the correlational analyses the data were aggregated over all test sessions [cf. (20,21)] and Pearson product moment correlations were calculated for each group. An alpha level of 0.05 was used in interpretation of statistical significance.

RESULTS

Labyrinth Integrity

All of the rats treated with intratympanic injections of sodium arsanilate (atoxyl) showed clear loss of the air-righting reflex and failed to show the normal righting response in the contact-righting test (see Table 1). When a Plexiglas sheet was lightly placed on the feet of supine atoxyl-treated rats, these animals reacted to the board as they would with respect to "real" ground, i.e., these rats would "walk" on the Plexiglas sheet while in the supine position. When challenged with vestibular stimulation by rotating the animals about a vertical axis, all of the normal rats (Group SHA) exhibited rotation-induced nystagmus, whereas none of the atoxyl-treated rats (Group VNX) did (Table 1).

Elevated Platform Test

The results of the elevated platform test revealed that the normal rats were able to stay on the platform for a significantly longer period of time ($p<0.01$) than the atoxyl-treated rats (Table 1). Failure to stay on the platform seemed to result from impaired control of balance in the labyrinthectomized rats.

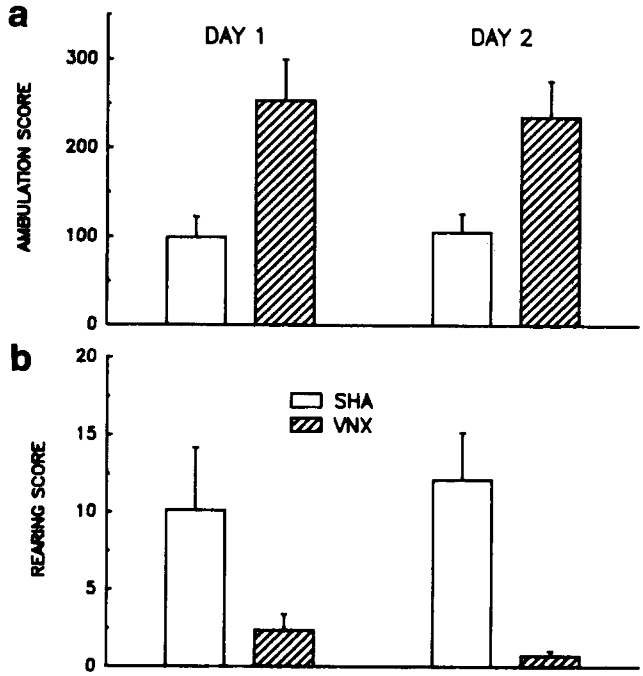

FIG. 1. (a, b) Group mean open-field ambulation and rearing scores on the two test days. Error bars are S.E.M.

Open-Field Behavior

The group mean number of sections entered in the open-field (ambulation score) on the first and second test day are shown in Fig. 1a. Inspection of this figure reveals that the labyrinthectomized rats ambulated approximately twice as much as the normal rats, on both days. Analysis of variance of these data supported this impression by revealing a significant drug treatment main effect, $F(1,17)=6.99$, $p=0.016$, but no significant days main effect and no significant interactions. Figure 1b depicts the group mean number of rearing responses observed on the two test days. Examination of these means shows that Group VNX exhibited many fewer rearing responses relative to the control rats. Statistical analysis indicated a significant drug treatment main effect, $F(1,17)=13.44$, $p=0.002$, but no significant days effect and no significant interaction. Analyses of the data for the defecation and grooming measures indicated no significant group differences ($p>0.10$) for these variables.

Correlation coefficients among the open-field variables and the elevated platform test scores for Group VNX and the control group are presented in Table 2. Significant within group correlation coefficients were obtained only in Group VNX for grooming with rearing, rearing with platform test scores, and grooming with platform scores ($ps<0.01$). In order to examine group differences in these correlation coefficient values a test for significance between two sample correlations was performed (6). Group VNX and Group SHA differed significantly in terms of correlations between open-field ambulation and grooming ($p<0.05$), rearing and grooming ($p<0.01$), rearing and platform test scores ($p=0.05$), and grooming and platform test scores ($p<0.01$). In general, grooming correlated positively with activity (ambulation and rearing) in Group VNX but negatively in the control group. As well, platform test scores for Group VNX correlated negatively with rearing and grooming, whereas Group SHA exhibited positive correlations.

TABLE 2

GROUP CORRELATION COEFFICIENTS FOR THE VARIOUS OPEN-FIELD BEHAVIORS AND THE LATENCIES FROM THE ELEVATED PLATFORM TEST

Variables	Rearing	Defecation	Grooming	Platform
Ambulation	**.482**	**−.372**	**.304**	**−.122**
	.474	−.051	−.656	−.463
Rearing	—	**−.474**	**.950**	**−.758***
		.016	−.193	.048
Defecation	—	—	**−.368**	**.293**
			−.072	−.245
Grooming	—	—	—	**−.783***
				.495

*$p<0.01$ (two-tailed test for r).

Note that the top number (bold) in each column is for Group VNX (labyrinthectomized) and the bottom number for Group SHA (control).

Activity in the Digiscan System

Horizontal activity measures. Figure 2a depicts group mean values for horizontal activity during each 20-min time bin on the two test days. Statistical analysis demonstrated no significant group difference ($p>0.10$) and only a weak trend toward greater activity in Group VNX during the second test session [drug treatment by days interaction, $F(1,17)=3.22$, $p=0.087$]. The movement time group means are shown in Fig. 2b and the statistical analysis revealed a significant drug treatment by days interaction, $F(1,17)=6.05$, $p=0.023$, demonstrating greater movement time in the control group than in the atoxyl-treated group on Day 1. Mean number of horizontal movements by each group revealed a complex relationship among the factors (see Fig. 2c). The analysis of variance produced a significant interaction of drug treatment by time bins by days, $F(2,34)=3.92$, $p=0.028$. In general, the labyrinthectomized rats displayed fewer horizontal movements than the control rats. Although the atoxyl-treated rats showed somewhat less movement time and fewer number of movements, they moved at a greater speed, especially during the initial time segments (see Fig. 2d). Statistical analysis of the speed data revealed a significant drug treatment by time bin interaction, $F(2,34)=3.25$, $p=0.05$. No significant group differences or interactions could be demonstrated for total distance travelled or average distance per movement.

Vertical activity measures. Group mean values for vertical activity during each 20-min time bin on the two test days are shown in Fig. 3a. Statistical analysis revealed a significant decrease in vertical activity over each test session [time bin main effect, $F(2,34)=78.02$, $p<0.001$] which differed for the two groups [drug treatment by time bin interaction, $F(2,34)=5.50$, $p=0.008$]. Post hoc tests indicated significantly less vertical activity in Group VNX during the first 20-min segment of each test session ($p<0.05$). Similar mean group values for vertical time are depicted in Fig. 3b. The analysis of variance indicated a significant decrease in vertical time over each test session [time bin main effect, $F(2,34)=36.48$, $p<0.001$] with Group VNX showing much less vertical activity time than the control group [drug treatment main effect, $F(1,17)=7.75$, $p=0.012$]. As well, the labyrinthectomized rats showed less of a decrease in this measure over the test sessions [drug treatment by time bin interaction, $F(2,34)=7.50$, $p=0.002$]. The two groups did not differ significantly in the number of vertical movements made, although both groups declined sharply on this measure over test sessions [time bin main effect, $F(2,34)=107.28$, $p<0.001$]. In contrast, when the average time taken per vertical movement was examined (see

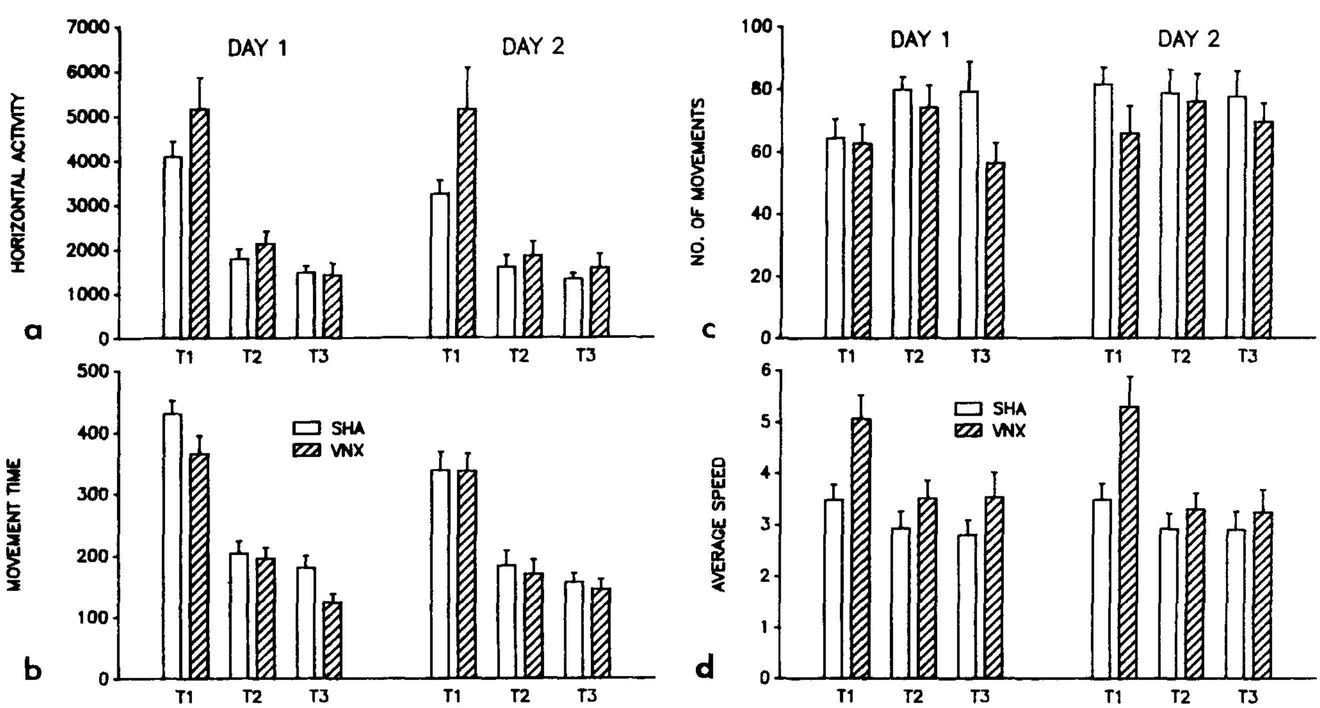

FIG. 2. (a, b, c, d) Group means for the Digiscan horizontal activity variables (horizontal activity, HA; movement time, MT; number of movements, NHM; average speed, AS) on the two test days as a function of test interval (T1–T3). Error bars are S.E.M.

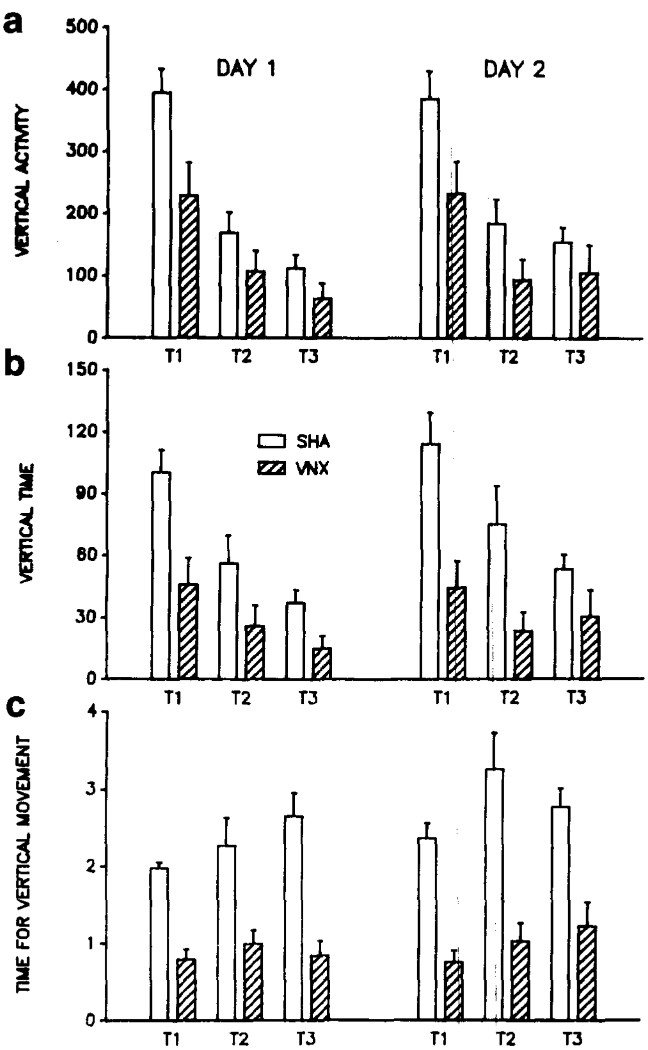

FIG. 3. (a–c) Group means for the Digiscan vertical activity variables (vertical activity, VA; vertical time, VT; average time per vertical movement, ATVM) on the two test days as a function of test interval (T1–T3). Error bars are S.E.M.

Fig. 3c), the atoxyl-treated group showed much lower values on this measure than the control rats [drug treatment main effect, $F(1,17)=31.54$, $p<0.001$]. In general, then, labyrinthectomy severely affected vertical activity, not by altering the number of rearing movements, but by drastically shortening the duration of these rearing responses.

DISCUSSION

Results from the tests for labyrinth integrity provided clear evidence for loss of vestibular function in the rats treated with sodium arsanilate. The animals from Group VNX exhibited loss of the air-righting and contact-righting (Plexiglas sheet test with supine rats) reflexes, whereas the saline-treated control rats showed normal behaviors in these tests. These finding are in agreement with previous studies which employed this chemical deafferentation procedure (5,30). In addition, when challenged with exposure to body rotation about a vertical axis, the control rats exhibited rotation-induced nystagmus, whereas the atoxyl-treated rats did not.

Histological examination of the degree of damage to the vestibular apparatus or the vestibular nerve was not carried out. However, previous studies have provided histological evidence for damage caused by treatment with sodium arsanilate (1,5) and these findings support the use of behavioral assays as criteria for successful labyrinthectomies. It should also be noted that the present study used a higher dose of sodium arsanilate (30 mg per side) than those used in previous studies (10–20 mg per side), increasing the likelihood of damage to the vestibular apparatus and nerve.

Loss of vestibular function produced some striking effects on behavior displayed in the open-field and the elevated platform tests. Labyrinthectomy resulted in a pronounced reduction in open-field rearing responses but an increase in ambulation scores, and the atoxyl-treated rats exhibited reduced proficiency in remaining on the elevated platform. The reductions in rearing incidence and the reduced time scores on the platform in Group VNX are perhaps not surprising, since loss of vestibular information would result in an inability to orient the head and/or body during execution of these behaviors. The resulting loss of control of balance would be expected to reduce the duration and/or frequency of rearing responses since the two-leg stance during rearing is far less stable than the four-leg stance during ambulation.

The increase in ambulation could represent a redirecting of exploratory behavior based on rearing responses, since ambulation and rearing are mutually exclusive behavioral categories. The increase in ambulation could also represent a redirecting of behavior towards sensorimotor systems still able to provide spatial information. With the loss of vestibular input, and probably reduced visual input (due to loss of the vestibulo-oculomotor reflex), a compensatory increase in proprioceptive feedback, generated by increased ambulation, may have provided the necessary information. This increased inclination to ambulate could also account for the group differences observed in the elevated platform test. With increased ambulation and impaired balance, the labyrinthectomized group would be at greater risk of falling off the platform.

The group differences in correlations obtained for the open-field behaviors and the elevated platform test may also be a reflection of the reduced ability to balance on the hind feet during rearing or even during grooming bouts. This suggestion is supported by the significant positive correlation between rearing and grooming in Group VNX. In addition, the significant negative correlations between the elevated platform test scores and both the rearing and grooming scores further support the contention that all three of these variables contain a balance ability component. Furthermore, Group SHA differed significantly from Group VNX in terms of the correlations between grooming with rearing and grooming with platform times. Although no significant group differences in frequency of grooming bouts were obtained, the correlational data would suggest that perhaps grooming duration or the complexity of grooming bouts might be reduced. Nonsystematic observations of grooming behavior in the open-field tests were consistent with this hypothesis.

Results of the multidimensional assessment of the behavioral effects of vestibular dysfunction in rats (Digiscan activity test) revealed some similarities to the observations obtained in the open-field test. Horizontal activity was increased in Group VNX during the first 20 min of the test sessions, a finding consistent with the increased ambulation observed in the open-field test. Similarly, vertical activity in the Digiscan system was significantly decreased during the first 20 min of the test sessions in Group VNX, an observation consistent with reduced rearing in the open-field. The present study did not distinguish between on- and off-wall rearing behavior [see (26)] and, given the deficits in balance in Group VNX, future studies should examine possible differences in these two categories of rearing in labyrinthectomized rats. One might expect that rats with vestibular dysfunction would be more likely to exhibit on-wall rearing in an attempt to stabilize their stance.

The Digiscan activity tests revealed some additional effects of atoxyl administration. Group VNX rats exhibited less movement time (both horizontal and vertical) and fewer number of horizontal movements but not vertical movements. The observation that speed of horizontal movements was greater for the atoxyl-treated animals during the initial time period in the test apparatus contrasts with the report that labyrinthectomized cats exhibit decreased locomotor speed (11). Especially striking in the present study was the large decrease in time per vertical movement shown by the labyrinthectomized rats. Most of these differences are compatible with the suggestion that loss of vestibular information produces a large deficit in ability to balance on the two hind feet during rearing responses. Exploratory behavior based on rearing activity might then be redirected toward horizontal activity and result in increased values for related variables in the Digiscan test. It should be noted that the rats in the present experiments were tested during the diurnal portion of their day-night cycles. Previous studies [e.g., (29)] have found that rats subjected to various experimental manipulations show increased abnormalities in behavior when tested at night, i.e., during their normal period of increased activity. Perhaps even more pronounced behavioral differences would be found in atoxyl-treated rats tested at night.

This study is the first multivariate assessment of the effects of chemical labyrinthectomy on spontaneous behavior in rats. Consistent with previous studies (9,10), behavioral deficits and changes were readily observed in the labyrinthectomized rats in the present experiment. An especially sensitive measure was the time per vertical movement (ATVM) variable in the Digiscan test. It would be of interest to determine which of the behavioral variables might show evidence of compensation at various time intervals following the lesion procedure and what role visual and other sensory cues might play in any observed compensatory changes in behavior. As well, the sodium arsanilate-induced labyrinthectomy procedure would seem to be an ideal preparation for investigation of the role of vestibular input in a variety of behavioral phenomena, such as spatial learning (12, 17, 24) and body rotation-induced motion sickness (3, 15, 16) and stress (4,18). The results from the present study, on effects of atoxyl on spontaneous behavior, should be helpful in interpretation of findings from future behavioral studies with this toxin.

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