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Sodium arsanilate-induced vestibular dysfunction in meadow voles (*Microtus pennsylvanicus*): effects on posture, spontaneous locomotor activity and swimming behavior

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Vestibular dysfunction was chemically induced in male meadow voles (*Microtus pennsylvanicus*) by intratympanic injections (30 mg per side) of sodium arsanilate (atoxyl). The control group received intratympanic injections of isotonic saline. After a one-week recovery period the voles were behaviorally assayed for integrity of their labyrinthine systems. All subjects were tested for the presence of the air-righting reflex and body rotation-induced nystagmus. Three weeks later a multivariate assessment of spontaneous motor activity of the voles was carried out in the automated Digiscan Activity Monitor. In addition, the swimming behavior of the voles was examined. Voles with vestibular dysfunction exhibited pronounced postural abnormalities (head dorsiflexion), were not able to swim with their nose above the water for a 1 min test period, and displayed disorientation and thrashing movements. In the Digiscan activity test the atoxyl-treated voles displayed significantly more activity in the horizontal measures ($Ps < 0.01$), including greater distance travelled per movement and greater speed of movements, relative to the control animals. The labyrinthectomized group also spent significantly ($P < 0.05$) less time in vertical movements and exhibited significantly more time in stereotypic behavior ($P < 0.01$), relative to controls. Atoxyl-treated voles also showed significantly less thigmotaxis (wall-hugging) than the control animals ($P < 0.01$). In general, changes in spontaneous behavior observed in the sodium arsanilate-treated voles were consistent with the presence of postural and balance abnormalities and a redirecting of exploratory vertical movements toward horizontal locomotion to the extent that these animals were clearly hyperactive in this dimension. The multivariate behavioral assessment available in the Digiscan Activity Monitoring system, thus seems to be especially useful in the examination of behavioral components affected by vestibular dysfunction.

INTRODUCTION

The vestibular 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 vertebrates can use for spatial orientation[16,23]. The vestibular apparatus is a structure common to all vertebrates and has 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. Thus, vestibular dysfunction has been found to have pronounced and long-lasting effects on behavior[23].

Results of previous studies have demonstrated ototoxic effects of a variety of agents in pigeons, mice, pigs, dogs and man[2,9,17]. Of special interest has been the arsenic derivative, sodium arsanilate[17], also known as atoxyl, which has been shown to be effective in chemically labyrinthectomizing rats[6,10,11,22,29] and guinea pigs[1,2]. Intratympanic injections of sodium arsanilate have been shown to result in vestibular nerve degeneration in the brainstem[1,2] with concomitant loss of labyrinthine righting and reduced postural support with exaggerated head dorsiflexion[10,11,22,29]. 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[1,2,9].

The effects of vestibular dysfunction on spontaneous locomotor behavior in rats has been previously examined in a multivariate fashion[22,24]. In general it was observed that chemically labyrinthectomized rats exhibited increases in horizontal activity measures (hyperactivity), especially early in the test sessions, and these horizontal movements occurred with greater speed[22,24].

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Vertical activity, in contrast, was much reduced, especially the time taken for individual vertical movements[22]. Labyrinthectomized rats also displayed greater levels of stereotyped behavior (stereotypy) and less thigmotaxis (wall-hugging behavior)[24].

Swimming ability has been previously used to assess vestibular integrity in monkeys[27], rats[30], mice[5] and toads[7]. When sodium arsanilate-treated rats were tested for swimming behavior[10], it was observed that drug application impaired several different parameters of swimming behavior. For example, atoxyl treated rats spent significantly more time underwater when swimming in a maze.

The present experiment examined the effects of intratympanic injections of sodium arsanilate on the behavior of a microtine rodent, the meadow vole (*Microtus pennsylvanicus*). Meadow voles are relatively small herbivorus rodents that, under long days (photoperiods), are diurnally active[13]. They are also excellent swimmers[26] and have been observed to swim long distances in their natural habitat[4]. As such, the effects of vestibular dysfunction on their swimming and locomotory behavior in their normally active period is of particular interest.

In the present study voles were treated with atoxyl or isotonic saline and subsequently tested for vestibular dysfunction by examination of the air-righting reflex and rotation-induced nystagmus. Swimming behavior[26] and spontaneous motor activity[20,28] were also examined. Spontaneous motor activity was assessed in a multivariate fashion in the automated Digiscan Activity Monitor.

MATERIALS AND METHODS

Subjects

Sixteen sexually mature male meadow voles (30–60 g, 1–2 months of age) were individually housed in polyethylene cages containing hardwood (Beta-chip) bedding and maintained at an ambient temperature of 20 ± 1 °C under a 12-h light/12-h dark photoperiod. Food (Purina Rat Chow and rabbit high fiber pellets) and water were freely available. All of the meadow voles were conceived in captivity by wild trapped or first generation laboratory born animals.

Digiscan activity monitors

The automated activity monitoring system consisted of 4 Digiscan Animal Activity Monitors (Omnitech Model RXYZCM-16, Columbus, Ohio). 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 11.5 cm above the floor of the boxes. Data were collected and analyzed by a Digiscan Analyzer (Omnitech Model DCM-8, Columbus, Ohio) which in turn transmitted the data to an IBM computer (AT286) with disk drive, where they were stored.

Chemical labyrinthectomy

Sodium arsanilate (atoxyl), an ototoxic compound[17], was injected intratympanically following the procedure of Horn et al.[10]. The voles were anesthetized with sodium pentobarbital (Somnotol, 65 mg/kg, i.p.). Eight male voles (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 over 3–4 s. Following each injection the ear canal was tightly packed with gelfoam. An additional 8 male voles 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 voles were tested for integrity of vestibular function. The first test examined the ability of the animals to right themselves in the air (air-righting reflex) when held supine and dropped from a height of approximately 30 cm onto a soft surface. A normal vole rights itself in the air, while falling, and lands on its feet. A vole with labyrinth dysfunction will tend to land on its back or side when tested in this manner. We also attempted to examine contact righting in the voles[22,29]. Another test examined the induction of rotation-induced nystagmus following 3 min of body rotation about a vertical axis at 70 rpm (see apparatus in Ossenkopp et al.[19]).

Digiscan Activity Monitor test. Three weeks after the tests of labyrinth integrity all animals were individually tested for spontaneous levels of locomotor activity. The voles were tested for 1 h in the late afternoon under light levels similar to those in the animal colony room. The Digiscan Analyzer collected data for each vole and cumulated these data into six 10-min time bins[20,21]. The system-differentiated behavioral variables recorded were (1) horizontal activity (HA), total number of beam interruptions for the lower set of infrared beams; (2) total distance (TD), the horizontal distance travelled by an animal in a given sample period; (3) number of horizontal movements (NHM), number of separate horizontal movements executed by the vole with a minimum stop time of 1 s to separate movements; (4) average distance (AD), mean distance travelled per horizontal movement (TD/NHM); (5) average speed (AS), mean distance travelled per unit time; (6) vertical time (VT) the amount of time the animal activated the upper set of beams; (7) number of vertical movements (NVM), number of separate vertical movements (rearing) separated by at least 1 s; (8) stereotypy time (ST), total time that stereotypic behavior (breaking the same beam(s)

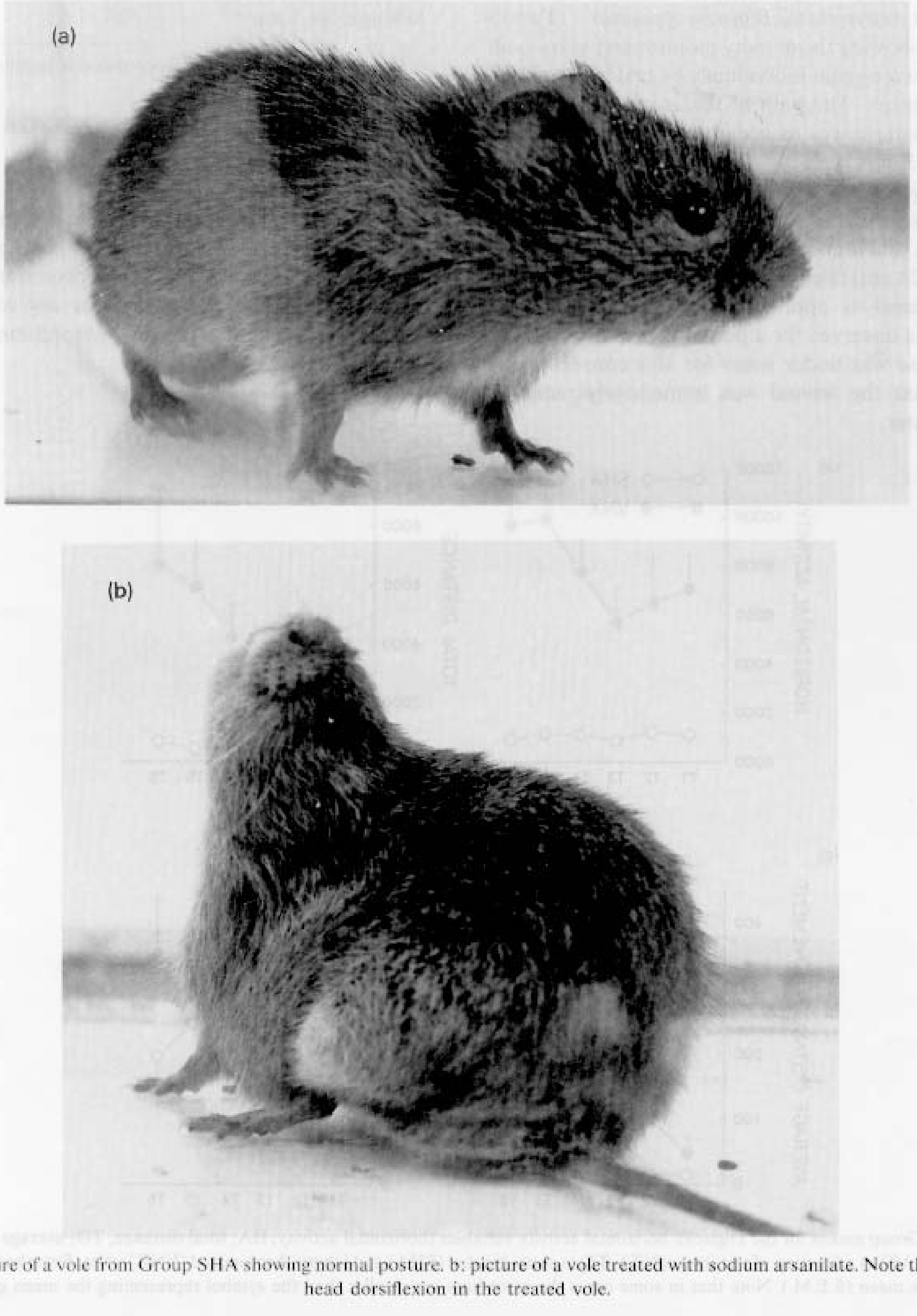

Fig. 1. a: picture of a vole from Group SHA showing normal posture. b: picture of a vole treated with sodium arsanilate. Note the pronounced head dorsiflexion in the treated vole.

repeatedly) occurred in a given time period; (9) number of stereotypic sequences (NSS), separate stereotypic movement sequences with a stop time of at least 1 s to separate sequences; (10) average time per stereotypic sequence (SST), mean time taken for each stereotypic sequence (ST/NSS); (11) center time (CT), time spent by the animal away from the walls of the cage (a measure of negative thigmotaxis).

Movement patterns in the Digiscan apparatus. Two to three days following the activity monitor test session all of the voles were again individually placed in one of the activity monitors. The path of the animal's horizontal movement pattern was recorded on an $X-Y$ plotter for a period of 3 min.

Swimming behavior test. One week after the Digiscan activity test all of the voles were tested for swimming ability. Each animal was placed in an aquarium (40 × 20 × 24 cm) filled with water to a depth of 15 cm and maintained at approximately 22 °C. Swimming behavior was observed for a period of 1 min unless the subject's nose was under water for 10 s consecutively, in which case the animal was immediately removed from the water.

TABLE I

Results of the tests for labyrinth integrity and the swim test

Test	*Groups*	
	SHA (n = 7)	*VNX (n = 6)*
Air-righting reflex	7/7[a]	0/6
Rotation-induced nystagmus	7/7	0/6
Swimming for 1 min	7/7	0/6

[a] Number of subjects in each group that successfully completed the test.

Data analysis

The data were analyzed with a mixed design repeated measures analysis of variance and post hoc comparisons used the Newman–Keuls procedure. In some cases a Rank–sum non-parametric test was used. An alpha level of 0.05 was used in interpretation of statistical significance.

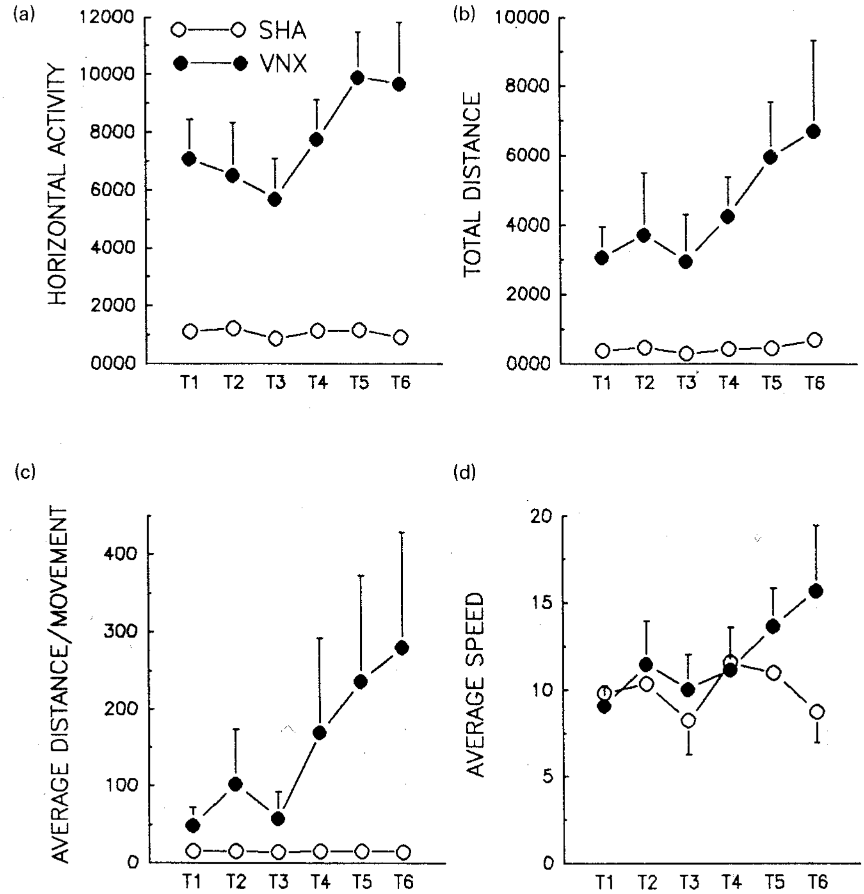

Fig. 2. (a–d). Group means for the Digiscan horizontal activity variables (horizontal activity, HA; total distance, TD; average distance, AD; average speed, AS) as a function of test interval (T1–T6) in sham-treated (SHA) and labyrinthectomized (VNX) voles. Error bars are standard errors of the mean (S.E.M.). Note that in some cases the error bars are smaller than the symbol representing the mean group value.

RESULTS

Two of the voles from Group VNX and one of the voles from Group SHA died prior to completion of all to the tests. Only the data from the remaining animals, that completed all of the tests, were used in the data analyses. Thus, group VNX had a group size of $n = 6$ and Group SHA had a size of $n = 7$.

Labyrinth integrity

All of the voles treated with intratympanic injections of sodium arsanilate showed clear loss of the air-righting reflex. When challenged with vestibular stimulation by rotating the animals about a vertical axis, all of the normal voles (Group SHA) exhibited rotation-induced head nystagmus which lasted approximately 4–5 s following cessation of the stimulus. None of the atoxyl treated animals showed this rotation-induced nystagmus (see Table I). When we attempted to place a Plexiglas sheet on the feet of supine atoxyl-treated voles to test for contact righting, it was found that the animals were too reactive to the handling procedure and would not stay in a supine position long enough to appropriately position the Plexiglas sheet. Thus, we were unsuccessful in obtaining data for this measure.

Postural changes. All of the atoxyl treated voles exhibited a pronounced dorsiflexion of the head when standing still (see Fig. 1b) and when moving had a strong tendency to show quick dorsal (vertical) thrusts of the head. None of the sham-treated voles showed any of these postural abnormalities (see Fig. 1a).

Activity in the Digiscan system

Horizontal activity measures. Fig. 2a depicts group mean values for horizontal activity during each 10-min time bin of the test session. Statistical analysis revealed

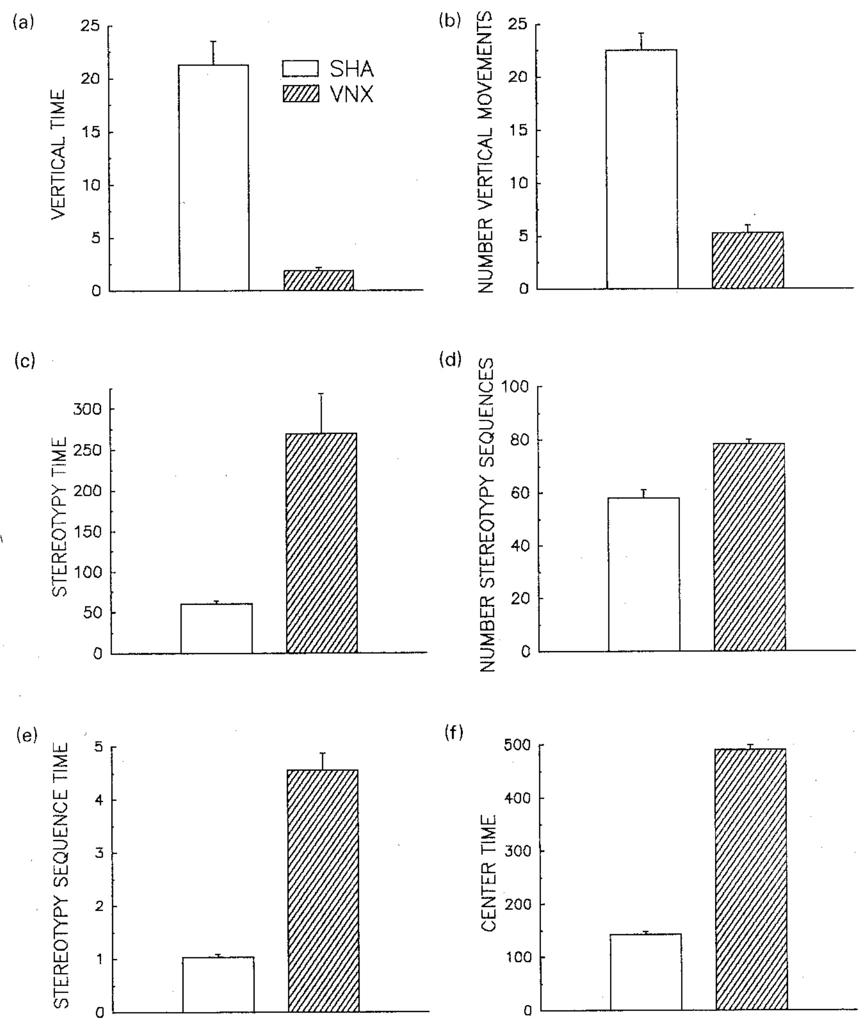

Fig. 3. (a–f). Group means for the Digiscan vertical activity, stereotypy, and thigmotaxis measures (vertical time, VT; number of vertical movements, NVM; stereotypy time, ST; number of stereotypic sequences, NSS; time per stereotypic sequence SST; center time, CT) in sham-treated (SHA) and labyrinthectomized (VNX) voles. Error bars are S.E.M.

a significant Group main effect ($F_{1,11}$ = 31.426, P < 0.001) and a significant Time main effect ($F_{5,55}$ = 2.795, P = 0.025). There was also a significant Group × Time interaction ($F_{5,55}$ = 2.713, P = 0.028) reflecting a general increase in activity over time in Group VNX but not in the SHA group. Mean total distance is shown in Fig. 2b. The analysis of variance indicated a significant Group main effect ($F_{1,11}$ = 8.203, P = 0.014), a significant Time main effect ($F_{5,55}$ = 3.766, P = 0.005), and a significant Group × Time interaction ($F_{5,55}$ = 2.812, P = 0.024). The interaction reflected a greater mean increase in total distance over the test session in Group VNX relative to Group SHA. Analysis of the mean number of horizontal movements displayed by each group revealed no significant main effects or interactions. In contrast, statistical analysis of the average distance per movement revealed a significant Time main effect ($F_{5,55}$ = 2.699, P = 0.029) and a significant Group × Time interaction ($F_{5,55}$ = 2.686, P = 0.03), but only a trend towards a Group difference ($F_{1,11}$ = 3.496, P = 0.085). These data are shown in Fig. 2c. Mean Group average speed data are depicted in Fig. 2d. Statistical analysis indicated a significant Time main effect ($F_{5,55}$ = 2.534, P = 0.038) and a significant Group × Time interaction ($F_{5,55}$ = 2.699, P = 0.029), but no group main effect (F < 1).

Vertical activity measures. Because of the large degree of variability in the vertical time and number of

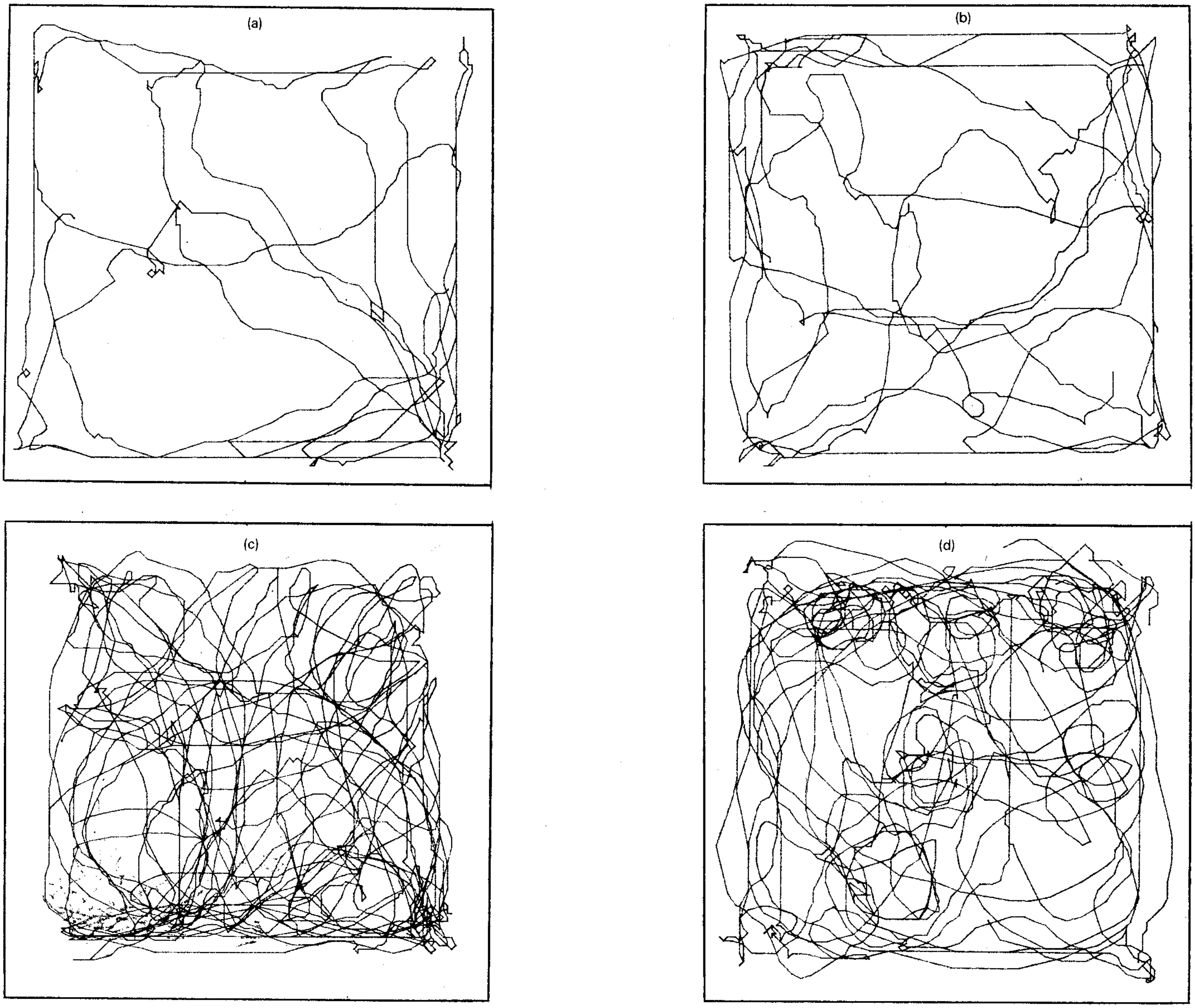

Fig. 4. (a–d). Two examples of horizontal movement patterns shown by sham-treated voles in the Digiscan appartus (a,b), and two examples of horizontal movement patterns by labyrinthectomized voles (c,d). These plotted path diagrams were collected over a 3-min period.

vertical movements measures, these were summed over the entire session and then compared with the non-parametric Rank Sum test. Vertical time was signficantly ($P < 0.05$) greater in Group SHA than in Group VNX. For the number of vertical movements there was only a trend toward a Group difference ($P < 0.10$). These data are presented in Fig. 3a and b.

Stereotypy and thigmotaxis measures. The variables of stereotypy time, number of stereotypic sequences, time per stereotypic sequence and center time (negative thigmotaxis) showed no signficant time main effects or Group × Time interactions. Thus, group mean values for the whole test session are presented in Fig. 3c–f. Significant Group main effects were obtained for stereotypy time ($F_{1,11}$ = 84.301, $P < 0.001$), time per stereotypic sequence ($F_{1,11}$ = 26.73, $P < 0.001$), and center time ($F_{1,11}$ = 67.51, $P < 0.001$). Number of stereotypic sequences showed only a trend toward Group differences ($F_{1,11}$ = 4.30, P = 0.06).

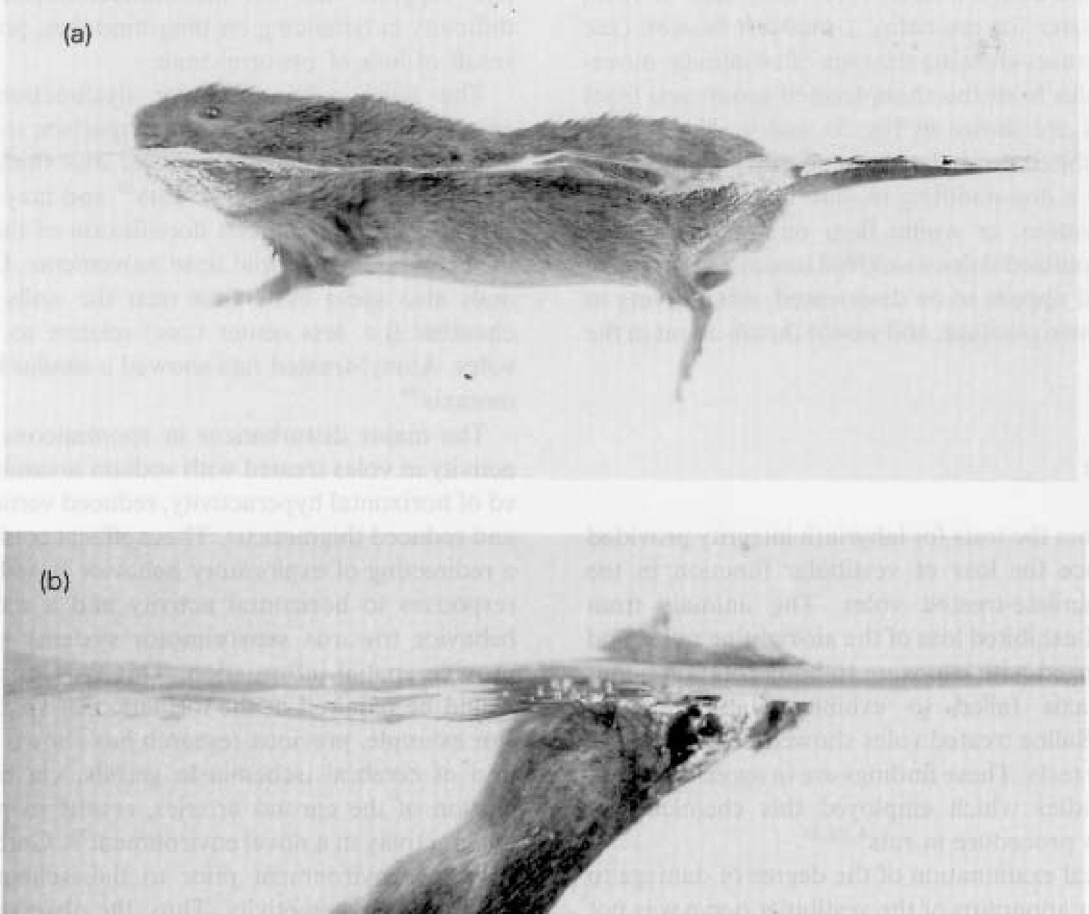

Fig. 5. a,b: pictures of a sham-treated vole (a) and a labyrinthectomized vole (b) swimming in the aquarium. Note the high degree of nose elevation in the control animal and the disoriented position of the labyrinthectomized vole.

Movement patterns in the Digiscan

Patterns of horizontal movement in the Digiscan test apparatus are shown for two typical voles from the sham-treated group (Fig. 4a and b) and for two representative animals from the atoxyl-treated group (Fig. 4c and d). Inspection of these patterns reveals much less movement by the two sham-treated voles, especially in the center of the open-field. The voles from Group VNX were not only more active, but also tended to show characteristic circling behavior.

Swimming behavior

None of the atoxyl-treated voles were able to swim above the water for the entire 1-min test session (see Table I). Pictures showing the type of swimming movements by voles from the sham-treated group and from Group VNX are shown in Fig. 5a and b. The control animals exhibited normal swimming movements, characterized by a dog-paddling motion and a high degree of nose elevation, or would float on the water. The labyrinthectomized voles would fail to stay on top of the water, would appear to be disoriented, often diving in an upside-down position, and would thrash about in the water.

DISCUSSION

Results from the tests for labyrinth integrity provided clear evidence for loss of vestibular function in the sodium arsanilate-treated voles. The animals from Group VNX exhibited loss of the air-righting reflex and when challenged with exposure to body rotation about a vertical axis failed to exhibit rotation-induced nystagmus. Saline treated voles showed normal behaviors on these tests. These findings are in agreement with previous studies which employed this chemical deafferentation procedure in rats[6,22,29].

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[1,6] 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 some of the previous studies (10–20 mg per side), increasing the likelihood of damage to the vestibular apparatus and nerve.

Results of the multidimensional assessment of the behavioral effects of labyrinthectomy on locomotor activity in voles (Digiscan activity test) revealed some striking effects. The labyrinthectomized voles exhibited increased horizontal activity levels, not in terms of number of movements but rather by making longer movements (distance and time) and increasing the speed of their movements over the test session. The observations of increased level of activity and increased speed of movements are consistent with previous studies in rats[22,24], but contrast with a previous report that labyrinthectomized cats exhibit decreased locomotor speed[14].

The present study also obtained less time spent in vertical movements in the atoxyl treated group. This finding also agrees with the data obtained for rats[22,24] and suggests that the labyrinthectomized voles had difficulty in balancing on their hind feet, probably as a result of loss of postural tone.

The voles with vestibular dysfunction exhibited greater stereotypic activity in comparison to the control animals. This finding is consistent with similar observations in labyrinthectomized rats[24] and may be partly a result of the pronounced dorsiflexion of the head and the accompanying rapid head movements. Control animals also spent more time near the walls of the test chamber (i.e. less center time) relative to the treated voles. Atoxyl-treated rats showed a similar loss of thigmotaxis[24].

The major disturbances in spontaneous locomotor activity in voles treated with sodium arsanilate consisted of horizontal hyperactivity, reduced vertical activity, and reduced thigmotaxis. These effects could represent a redirecting of exploratory behavior based on rearing responses to horizontal activity and a redirecting of behavior towards sensorimotor systems still able to provide spatial information. This type of information would be required in the formation of spatial maps[16]. For example, previous research has shown that induction of cerebral ischemia in gerbils, via bilateral occlusion of the carotid arteries, results in pronounced hyperactivity in a novel environment[31]. Gerbils familiar with the environment prior to the ischemia did not exhibit this hyperactivity. Thus, the observed hyperactivity may have represented a reduction of the ischemic animal's ability to form spatial maps. Given the importance attached to angular velocity signals from the vestibular system in landmark learning and sense of direction[16], the hyperactivity observed in the labyrinthectomized voles in the present experiment may also represent such an inability to form spatial maps.

The observed disturbances in swimming behavior are consistent with previous reports on rats treated with sodium arsanilate[10]. These findings are of special interest since meadow voles are normally very adept swimmers and are able to float for considerable periods of time. The treated voles in the present study were very disoriented when placed in the water, having great difficulty in determining the direction of gravitational pull. As a result the animals would often swim upside down or thrash about in the water while turning about their major body axis (corkscrew turning movement). These observations are also consistent with the failure to observe an air righting reflex in these animals.

The present study is the first multivariate assessment of the effects of chemical labyrinthectomy on spontaneous behavior in predominantly diurnally active meadow voles. Consistent with previous studies in rats[10,11,22,24] behavioral deficits and changes were readily observed in the atoxyl treated animals in the present study. This sodium arsanilate-induced labyrinthectomy procedure would seem to be an ideal preparation for investigation of the role of vestibular inputs in a variety of behavioral phenomena, such as spatial learning[15,18,25] and body rotation-induced motion sickness and stress[3,8,12,19]. The results from the present study should be helpful in interpretation of findings from future behavioral studies in voles treated with sodium arsanilate.

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