Pharmacology Biochemistry and Behavior, Vol. 56, No. 4, pp. 643–648, 1997
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0091-3057/97 $17.00 + .00

PII S0091-3057(96)00515-1

Effects of Aluminum Exposure on Behavioral Parameters in the Rat

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Received 29 September, 1995; Revised 22 April 1996; Accepted 8 June 1996

STRUYS-PONSAR, C., A. KERKHOFS, A. GAUTHIER, M. SOFFIÉ AND PH. VAN DEN BOSCH DE AGUILAR. *Effects of aluminum exposure on behavioral parameters in the rat.* PHARMACOL BIOCHEM BEHAV **56**(4) 643–648, 1997.—Adult rats were treated by intraperitoneal injection of aluminum gluconate for 3 months. Rats were submitted to the radial maze test to determine the influence of chronic aluminum intoxication on cognitive and noncognitive behavioral processes. Both learning abilities (working memory and reference memory) and rapidity (time spent to respond and to master a trial) were analyzed. Aluminum concentration was evaluated in the brain, serum, and liver to assess aluminum body burden. While hippocampus and neocortex showed a significant increase in aluminum concentration, aluminum treatment did never affect the animal's performance during cue learning or when the insert cues were removed. The only behavioral difference observed was a decrease in rapidity: both the total time to finish a trial and the latency to make the first choice were lengthened in aluminum-intoxicated rats. © 1997 Elsevier Science Inc.

Aluminum gluconate Rat Brain aluminum Radial maze Spatial memory Latency

ALUMINUM (Al) is a ubiquitous element naturally present or anthropogenetically introduced into our environment, and it has no known biological or biochemical functions. For many years, Al was thought to be innocuous and largely unabsorbed from the gastrointestinal tract (14). However, when the gastrointestinal barrier is bypassed or renal excretion is impaired, or in rare cases of occupational exposure, Al accumulates in tissues, impairing their functions in various ways. Acute toxicity (anemia, osteomalacia, and encephalopathy) appeared in patients with chronic renal failure who were treated by haemodialysis and by Al-containing medications (1–3,15,26). Chronic exposure to Al dust has been implicated in the emergence of impaired cognition in miners who were accidentally exposed at their workplace (12,13,17–19,22) or were iatrogenically exposed to the metal as means of prophylaxis of silicosis (25). It also appears that Al could be implicated in the aetiology of several progressive neurodegenerative disorders. A neurotoxic injury involving calcium, Al, and silicon has been demonstrated to play a crucial role in the pathogenesis of Pacific amyotrophic lateral sclerosis–Parkinson's disease syndrome (11,16,30). In contrast, the role of Al in the aetiology and the pathogenesis of sporadic cases of Alzheimer's disease (AD) is based on a large body of observations and findings (7,10,21,31), many of which are still controversial (5,9). To date, attempts to confirm the "Al hypothesis" in AD have been inconclusive and contradictory. No clear evidence has been obtained that Al toxicity could lead to progressive dementia or Alzheimer's disease, and, moreover, the behavioral sequelae of chronic Al accumulation have yet to be studied extensively.

The purpose of this study was to test a possible effect of chronic Al intoxication on cognitive and noncognitive behavioral processes. Rats were intraperitoneally injected with Al gluconate over a period of 3 months. Both learning abilities (working memory and reference memory) and rapidity (time spent for ending a trial) were analyzed in a radial maze. Finally, the serum, liver, and brain aluminum content was assayed to estimate Al body burden.

EXPERIMENTAL APPROACH

Rats

Male rats of the Wistar strain, 2 months of age and 247.2 ± 14.4 g in weight (mean ± SEM, $n = 29$) at the beginning of

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TABLE 1
ALUMINUM CONCENTRATION

	Control	Al 2m	Al 2m + 1m	Al 3m
Serum	10.89 ± 1.21[a]	ND	ND	151.30 ± 10.50[b]
Brain	0.36 ± 0.06[a]	1.25 ± 0.19[b]	0.87 ± 0.13[c]	1.48 ± 0.21[b]
Liver	0.20 ± 0.06[a]	7.303 ± 1.03[b]	6.197 ± 1.26[b]	8.89 ± 2.81[b]

The table presents aluminum concentrations in the serum, brain, and liver of rats intraperitoneally injected with sodium gluconate for 3 months (Control) or with aluminum gluconate for 2 months (Al 2m), for 3 months (Al 3m), or for 2 months with 1 month rest (Al 2m + 1m). Values are expressed as mean ± SEM, in units of μg/g tissue wet weight or μg/liter of serum. Means in the same line with a different letter are significantly different (Scheffé's F-test, $p < 0.05$). ND, not done.

the treatment, were used in this study. The rats were housed in propylene cages (Iffa Credo, Brussels, Belgium) under standard conditions (20°C, 50–70% humidity, and 12 L:12 D cycle). They were given free access to food (UAR, Animalabo, Brussels, Belgium) and tap water. Aluminum gluconate was prepared by dissolving Al chloride hexahydrate extrapure and sodium gluconate (both Merck, Schuchardt, FRG) in ultrapure water (Milli-Q water purification system; Millipore, Bedford, MA, USA) with 1:1 stoichiometry. Al gluconate (0.667 mg of Al/250 μl) was injected into the rats intraperitoneally three times per week ($n = 19$); control rats ($n = 10$) received an equal volume of vehicle (sodium gluconate). The treatment began 2 months before behavioral testing and was maintained throughout maze learning to avoid any decrease in tissue Al concentration (Table 1). Injections were always made in the afternoon after the maze trials.

No significant difference in body weight was observed at the end of the 2 months of treatment: group averages (means ± SEM) were 317.2 g ± 3.6 for Al-treated rats and 337.6 g ± 9.7 for control rats. Most rats gained weight over the course of the treatment. Prior to the radial maze experiment, the body weight of the rats was reduced by food deprivation and maintained at 80% of their free-feeding value throughout the experiment.

Radial Maze Test

Apparatus and procedure. The apparatus was an elevated (80 cm above the floor) eight-arm radial maze made of grey PVC. Each arm was 78 cm long, 8 cm wide, and 0.5 cm high. The arms were equally distant from each other and were attached to a central area 60 cm in diameter. A circular food well (2 cm in diameter, 1 cm deep) was positioned at the end of each arm. Four of the eight arms were baited (one 45-mg Noyes food pellet). The four baited arms were always in the same position (2, 3, 5, 7) and were differently distant from each other (Fig. 1) to avoid any systematic response such as visiting adjacent or equidistant arms. During the first phase of the test, cue learning, the four baited arms were covered with different-textured insert cues (strips of balatum). During the second phase, place learning, the positions of the four baited arms did not change, but the insert cues were removed and the eight arms become identical. The baited arms were only recognizable by their location (according to extramaze cues present in the experimental room); thus, correct choices required the use of a spatial map. The apparatus was carefully cleaned before each trial. Rats were tested individually in both phase 1 and phase 2. They were first submitted successively to 50 trials in phase 1 (the cue learning test) followed immediately by 10 trials in phase 2 (the place learning test). Each rat received two trials daily. A trial ended when the rat had found and consumed the four pellets or when 10 min had elapsed.

Data collection and statistical analyses. Five measures were submitted to statistical analysis: a) total number of errors (i.e., the total number of arms visited minus the number of visits to baited arms); b) working memory (WM; i.e., the number of visits to baited arms divided by the number of visits and revisits to baited arms)—this measure represents an index of short-term memory or WM, which, according to Olton and Samuelson (23), is defined as the ability to remember which arms had already been visited during a given trial; c) reference memory (RM; i.e., the total number of visits to baited arms divided by the total number of different arms visited)—this measure is an index of long-term memory, which is defined as the ability to remember which are the baited and which the nonbaited arms; contrary to WM, RM is stable information relevant during the whole learning process; d) total time (time to end a trial, i.e., to obtain the four pellets); e) first choice latency (i.e., the time elapsed before the first entrance into a baited or nonbaited arm).

Data were grouped into six blocks of 10 trials for the five variables. Al treatment effect was computed by analysis of variance (ANOVA) for repeated measures for all the variables. The analyses were computed for the cue learning (five blocks of 10 trials). The incidence of the removal of insert cues was tested by comparing blocks 5 and 6 (i.e., the 10 trials before and after removal of the cues).

Aluminum Evaluation

The day after the test, Al concentration was estimated in control and Al-treated rats in serum, brain, and liver by graphite furnace atomic absorption spectrometry (GFAAS). Rats were anesthetized with ether, and blood from Al-treated rats ($n = 27$) and control rats ($n = 9$) was collected by intracardiac puncture into 5-ml tubes (Venoject, Terumo Europe N.V., Leuven, Belgium) using Plastipak needles and syringes (both Becton Dickinson & Co.). After centrifugation for 20 min at $2000 \times g$, serum was collected for analysis. Then the rats were killed by decapitation, and the liver (the same lobe in each animal) was carefully dissected (control rats: $n = 6$; Al-treated rats: $n = 12$). The following brain areas ($n = 6$ for control; $n = 4$, $n = 5$, and $n = 4$ for rats treated with Al for 2 months, for 2 months with 1 month of normal diet, and for 3 months, respectively) were dissected on a chilled plate: olfactory bulbs; anterior olfactory nuclei; frontal, parietal, and temporal cortex; hippocampus; cerebellum; and spinal cord. Tissue samples (around 80 μg of weight) were placed in 5-ml propylene gradu-

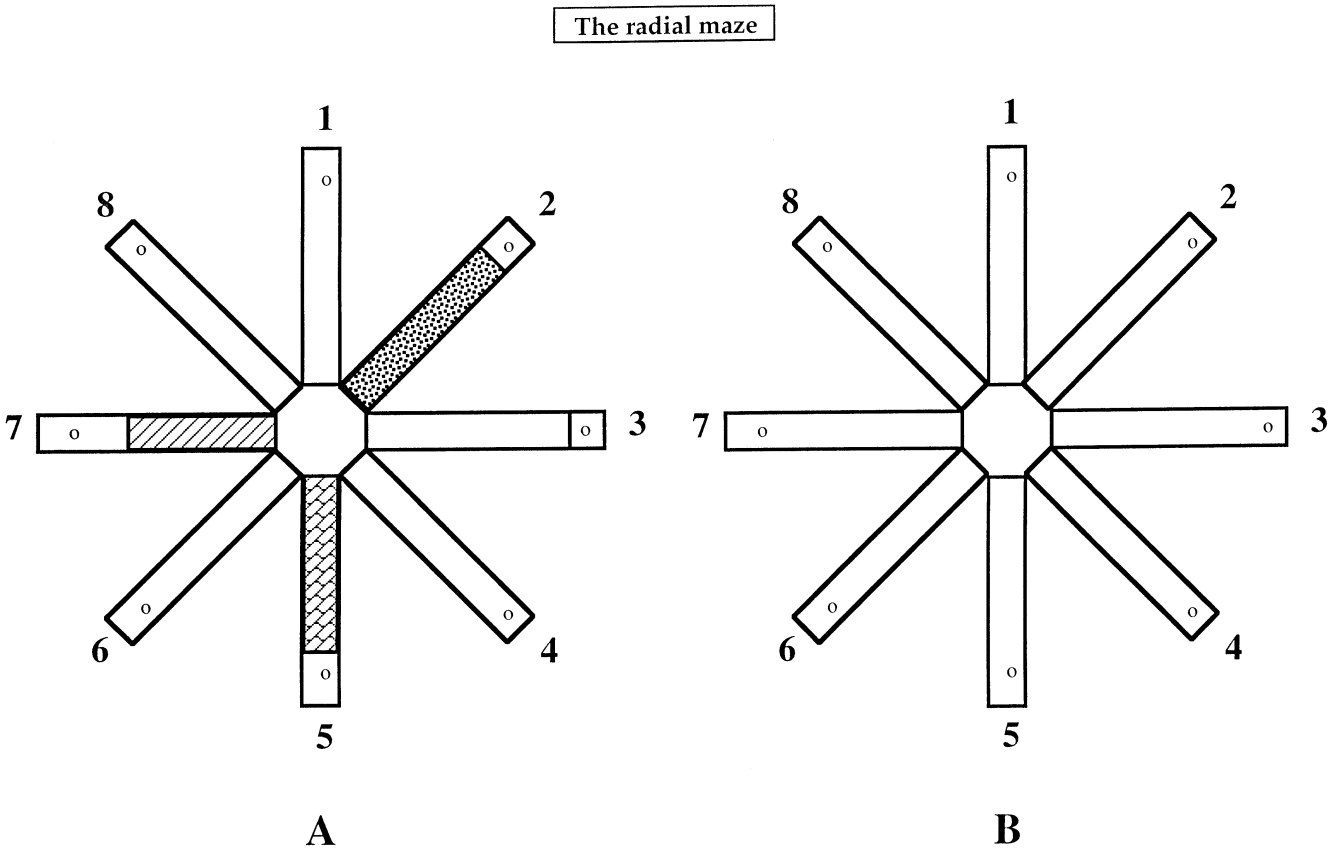

FIG. 1. Schematic representation of the eight-arm radial maze. The baited arms are 2, 3, 5, and 7.

ated tubes with polyethylene caps (Biolab, Limal, Belgium). These tubes were previously washed in hydrochloric acid and then in 1% nitric acid (Merck) for a week and rinsed in ultrapure water. The wet digestion method of van Ginkel et al. (29) was used. Tissue specimens were heated in 1 ml of 65% nitric acid Suprapur R (Merck) at 70°C and were recovered in 4 ml in 1% nitric acid. The aqueous standard method was used for the determination of Al. Great care was taken to avoid any contamination. The concentration of Al was measured by GFAAS (Varian AA 1275 series) with deuterium background correction. The atomic absorption signal was measured by integrating the total absorption profile at 309.3 nm with a spectral bandwidth of 0.5 nm. All the analyses were performed in triplicate, and the results were expressed in μg/g tissue wet weight or in μg/liter of serum.

Data were analyzed by three-way ANOVA for the brain (treatment, region, and rat) within the SAS general linear model program. Tests for least significant differences were applied when significant ($p < 0.05$) differences among treatments existed. Data from the serum and liver were analyzed by one-way ANOVA. Comparisons were done by Scheffé's F-test ($p < 0.05$).

RESULTS

Aluminum Evaluation

Al increased in the serum, brain, and liver (Table 1). At the end of treatment, the serum Al level was 151.3 ± 10.5 μg/liter in rats treated with Al for 3 months and 10.9 ± 1.2 μg/liter in control rats [$F(1, 16) = 152.212$, $p = 0.0001$].

Al concentration in the brain increased in the Al-treated rats [ANOVA 3, treatment effect, $F(3, 99) = 33.52$, $p = 0.0001$]. It should be noted that the rats who did not receive the Al gluconate treatment in the third month had a significant decrease in brain Al concentration. As a result, Al treatment had to be continued during the behavioral test (third month) to avoid any decrease in brain Al concentration. The incremental Al concentration was 240% for rats treated with Al for 3 months when compared with control rats.

Al increase differed from one region of the brain to another [ANOVA 3, region effect, $F(7, 99) = 35.59$, $p = 0.0001$; Fig. 2]. Among all the brain areas studied, the hippocampus, temporal cortex, and anterior olfactory nucleus showed the highest levels of Al, followed by the parietal cortex, frontal cortex, and olfactory bulbs (Scheffé's F-test, $p < 0.05$). The spinal cord and cerebellum showed the lowest levels of Al and were not significantly affected by Al accumulation. By far, the liver showed the highest Al concentration: 44-fold higher in Al-treated rats than in controls (ANOVA 1, $F(3, 17) = 8.3$, $p = 0.002$).

Aluminum Effects on Behavioral Parameters

Al treatment did not affect the rat's performance during cue learning [neither treatment nor interaction between treatment and blocks (group of 10 trials), for number of errors, WM, and RM]. No significant difference emerged between

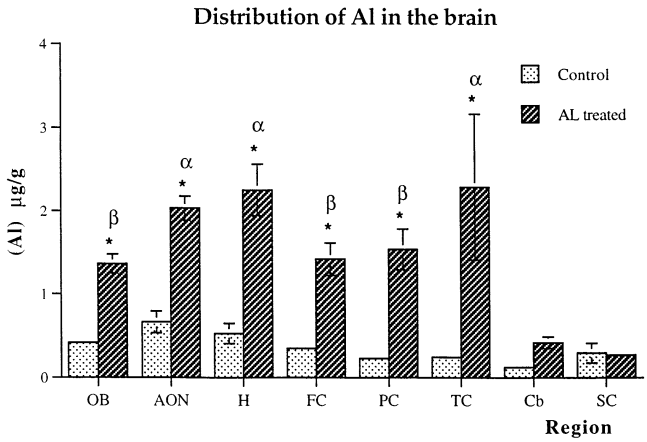

FIG. 2. Brain distribution of aluminum after administration of aluminum gluconate (Al treated) or sodium gluconate (Control) for 3 months. Brain regions: olfactory bulb (OB), anterior olfactory nucleus (AON), hippocampus (H), frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), cerebellum (Cb), and spinal cord (SC). Values are expressed as mean ± SEM. *Significant difference between treatment and control (Scheffé's F-test, $p < 0.05$). Means with a different letter (α or β) are significantly different from each other (Scheffé's F-test, $p < 0.05$).

the Al treated and control rats; in both groups, performance improved with time [ANOVA, block effect, $F(4, 72)$ for errors = 94.56, $p < 0.0001$; for WM = 18.84, $p < 0.0001$ and for RM = 116.82, $p = 0.0021$]. Again, neither a treatment effect nor a treatment and blocks interaction was found (Fig. 3).

However, effects of Al treatment did emerge if the time needed to master the task (total time; Fig. 4) or the time to enter an arm (first choice latency; Fig. 4) was considered. There was no significant difference in the amount of time needed for the control and the Al-treated rats during the 10 first trials (block 1). However, in the following 40 tests (blocks 2–5) a significant difference appeared: the Al-treated rats required more time during cue learning [ANOVA, treatment effect, blocks 2–5, $F(1, 18) = 4.65$, $p = 0.048$]. A similar trend was observed in the first choice latency parameter during cue learning. Al-intoxicated rats required more time to make the first choice during cue learning than did the control rats [ANOVA, blocks 2–5, $F(1, 18) = 5.56$, $p = 0.030$]. In the final 10 trials, after the cue removal, the performance of the Al-treated rats differed from that of the control rats [ANOVA, block 6, ($F(1, 18) = 5.83$, $p = 0.027$]. The Al-treated rats needed more time to make the first choice than the control rats during place learning.

DISCUSSION

Several cognitive and noncognitive parameters were employed to determine the neurotoxic effects of chronic Al exposure in adult rats. Concurrently, Al concentration was analyzed in these rats.

The results indicate that there was a significant Al accumulation not only in the serum and liver but also in the brain of rats treated with Al. In the brain, Al accumulation was region specific: the highest levels were observed in the temporal cortex, anterior olfactory nucleus, and hippocampus. Average levels were found in the frontal and parietal cortex. The lowest levels were observed in the cerebellum and spinal cord. In these areas, Al concentrations were not significantly different between Al-treated and control rats.

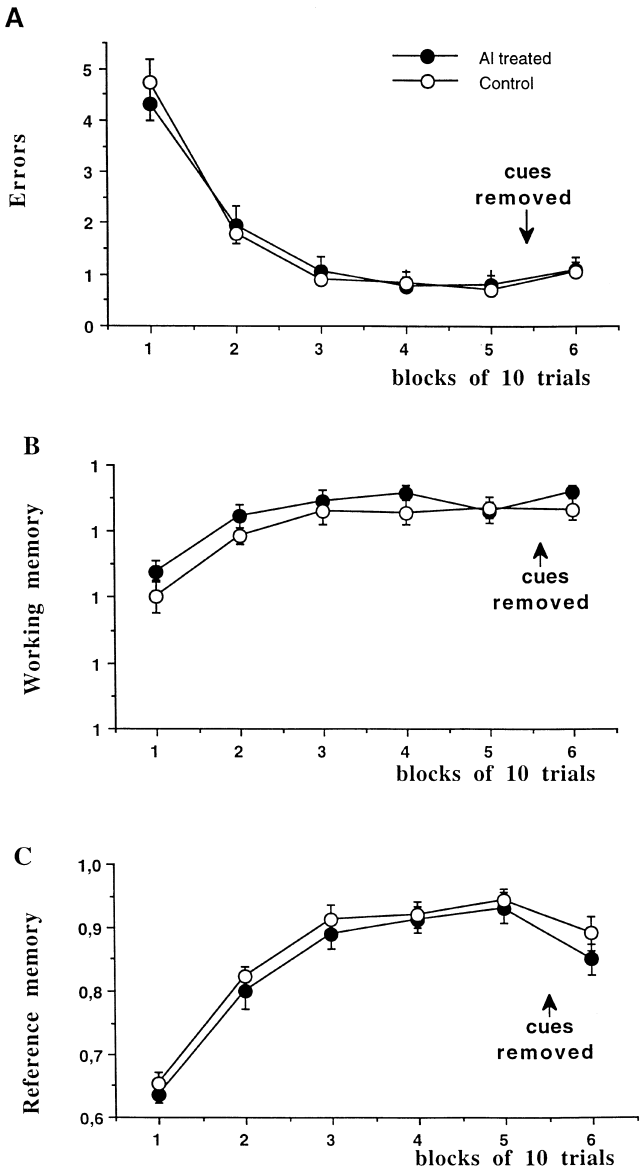

FIG. 3. Number of errors (A), scores for working memory (B), and scores for reference memory (C). Values are mean ± SEM.

The absence of cognitive impairment in Al-treated rats was at first unexpected in light of the treatment and regional brain effects observed. The hippocampus has been shown to be preferentially susceptible to a wide variety of toxic insults following exposure to environmental toxicants such as lead or abuse of drugs such as alcohol or excitotoxic amino acids. Numerous studies (20,24) have shown that spatial tasks are sensitive to both hippocampal and neocortical (parietal and medial frontal cortex) damage. Although comparisons between our experiments and other studies are of limited significance because of the different forms of intoxication, it is interesting to underline the behavioral discrepancies and similarities observed in these various studies. For example, an impairment in the eight-arm maze is reported in prenatally treated mice (27) but not in newborn treated rats (6) nor in young rats after chronic oral Al treatment (8). Unfortunately, all these radial maze studies used a procedure in which the

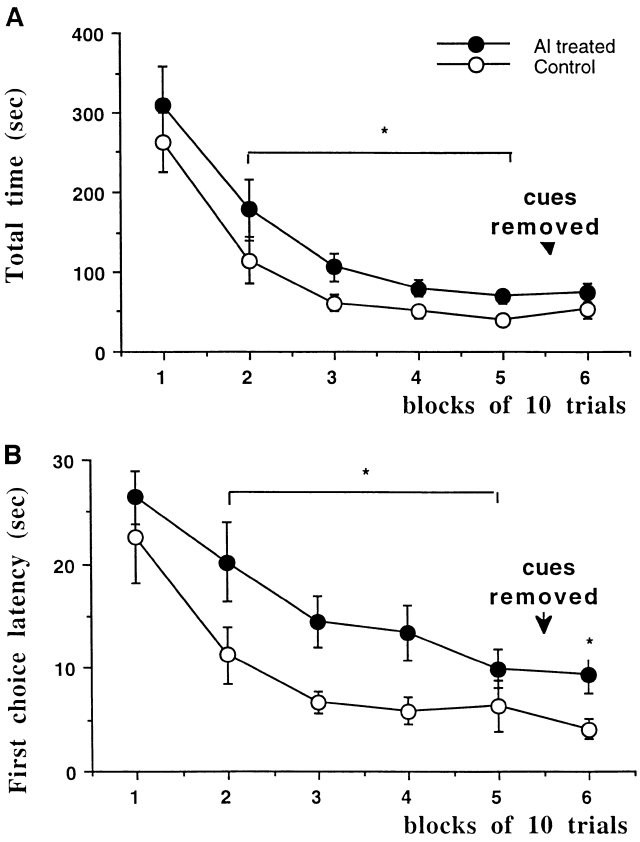

FIG. 4. Time to finish a trial (A) and to make the first choice (B) for aluminum-treated and control rats. Values are mean ± SEM. *Significantly different from control rats ($p < 0.05$).

eight arms were baited. Moreover, none of them analyzed the sequence of arms visited (i.e., systematic response or not). Therefore, the cognitive involvement, i.e., the implication of working memory, appears questionable.

In our experiment, one methodological criticism that might be raised is that we adopted a procedure in which cue learning preceded place learning. This procedure was chosen to test a possible interaction between Al intoxication and visuomotor coordination, a phenomenon reported in human subjects having high serum Al levels (4). Our results allow us to rule out a deficit in visuomotor coordination. However, we cannot exclude the possibility that the progressive learning might have reduced the differences during place learning. Indeed, the rat had the possibility to take in spatial information during 50 trials of cue learning, and consequently the spatial place trials occurred in well-trained rats. However, in our procedure, in spite of the reduced difficulty of the task due to progressive learning, the rat could not succeed without adopting cognitive responses involving working memory and/or spatial memory.

The only significant difference observed in Al-intoxicated rats was a delay in the decision to make a first choice and a lengthening in the time to finish a trial. A slowing down of motor activity (recorded in open field) was reported in adult Al-treated rats (28), and a lengthening of the total trial time in the eight-arm maze was reported in Al-intoxicated rats by Cherroret et al. (6) and Santucci et al. (27). These authors proposed three hypotheses to explain the increase in time to realize a trial: an impairment in sensory inputs or processing, an impairment in motor abilities, or a general drop in basal metabolism.

Although it is difficult to distinguish between locomotor and cognitive components in learning tasks, the present results allow us to rule out a motor impairment and reinforce the hypothesis of an impairment in sensory inputs or processing. Al-intoxicated rats required more time to finish a trial, not at the beginning of learning, but only when they became able to master the task. Direct qualitative observations revealed that Al-intoxicated rats ran and turned in the maze as well and as quickly as control rats. Finally, the increase in both first latency and total time to achieve a trial is mainly due to hesitation of Al-treated rats before entering an open arm.

At this stage of the study, it would be speculative to propose a specific interpretation. Further study is needed to clarify the relations between aluminum accumulation and behavior.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Belgian Incentive Program "Health Hazards" initiated by the Belgian State Prime Minister's Service, Science Policy Office, and by a grant from the "Action Concertée" (number 9297-158) from the Ministry of the Belgian French Community. The scientific responsibility is assumed by the authors.

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