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Intracerebroventricular but Not Intraperitoneal Administration of Aluminum Attenuates Vasopressin-Enhanced Retrieval of a Passive Avoidance Task in Rats

HANS-GERT BERNSTEIN,*[1] HELMUT SCHWARZBERG,† GERD POEGGEL‡ AND MICHAEL REISER‡

*Institutes for *Anatomy and †Physiology, Medical Academy Magdeburg, Leipziger Str. 44, D(O)-39120 Magdeburg, Germany*
‡Institute for Neurobiology, Magdeburg, Germany

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BERNSTEIN, H.-G., H. SCHWARZBERG, G. POEGGEL AND M. REISER. *Intracerebroventricular but not intraperitoneal administration of aluminum attenuates vasopressin-enhanced retrieval of a passive avoidance task in rats.* PHARMACOL BIOCHEM BEHAV 47(3) 587-590, 1994.—We studied the influence of single intracerebroventricular (ICV) and intraperitoneal (IP) injections of the neurotoxin aluminum on the retrieval of a passive avoidance task in rats and on the vasopressin-evoked improvement of the recall of the task. It was found that ICV administration of the metal alone strongly decreases the retention time of a passive avoidance task, whereas IP application of aluminum prolongs it. Vasopressin given ICV and IP leads to an enhancement of retrieval (prolongation of the retention time). Vasopressin in combination with aluminum does not improve the recall of the task when both substances are given ICV. Intraperitoneal injection of the neuropeptide together with the metal improves the recall of the task. Our data point to the crucial importance of the route of application of aluminum for behavioral studies.

Aluminum Vasopressin Rat behavior Passive avoidance memory Retrieval Intracerebroventricular injection Intraperitoneal injection

ALUMINUM (Al) is a well-established neurotoxin in man. The metal is apparently involved in the pathogenesis of dialysis dementia and, very likely, of senile dementia of Alzheimer type, Parkinson-dementia syndrome of Guam type, as well as of amyotrophic lateral sclerosis (2,11,14). In studies with rabbits, it has been shown that after Al administration there develops a SDAT-like neuropathy, including the formation of neurofbrillary tangles and massive deficits in learning and memory (8,15,19). Although the neurotoxic effects of the metal are possibly less pronounced in rats, aluminum-induced neurobehavioral impairment can be found in this species, too (8,12,19). In the endeavour to simulate certain aspects of aluminum-induced human disorders by appropriate animal paradigms almost all investigations on the influence of the metal on higher brain functions have been performed after chronic exposure of the metal. Hence, little is yet known about possible acute actions of aluminum on the rat's central nervous system. Very recently, Peng and coworkers described a profound influence of a single dose administration of aluminum on the cholinergic neurotransmitter enzyme system, thereby showing that the toxic action of Al may well be acute (13).

We were interested in elucidating whether aluminum is capable of evoking acute effects of the recall of a stored information in rats, and whether the well-documented improvement of avoidance behavior by vasopressin (6,10,16) is altered by the neurotoxin.

[1] Requests for reprints should be addressed to Dr. Hans-Gert Bernstein, Institute for Anatomy, Medical Academy, Leipziger Str. 44, D(O)-39120 Magdeburg, Germany.

This report shows that Al is capable of modulating vasopressin-induced effects on the retention of a passive avoidance task in rats, depending on the route of administration of the neurotoxin.

METHOD

Subjects

A total of 68 Wistar male hooded rats obtained from a local breeding colony weighting about 250 g served as subjects. Animals were housed individually in plastic cages in a room maintained at 22°C and on a 12 L : 12 D schedule. Free access to food and water was permitted at all times.

Learning Experiment and Drug Administration

Part of the rats were anaesthetized with hexobarbital (150 mg/kg, IP). A stainless steel cannula for ICV application was inserted into the lateral cerebral ventricle and fixed with dental cement and acrylate. A 5-day recovery period was allowed before starting behavioral experiments.

One-trial learning step-through passive avoidance behavior was used (1,17). The experimental arrangement consisted of an illuminated platform attached to a dark compartment with a grid floor. Rats were placed on the platform and allowed to enter the dark compartment. Because rats prefer dark to light they normally entered within 10 s.

After an additional trial on the following day, an unavoidable electric foot shock from the stimulator (pulse with 2 ms, frequency 100 Hz, train duration 3 s, current 2 mA) was delivered through the grid floor. Animals were then subdivided into different subgroups and received $AlCl_3$, AVP, and/or saline, either ICV or IP, according to the time scheme shown in Table 1.

Regardless the route of injection of $AlCl_3$ and vasopressin, animals were subjected to a passive avoidance trial 24 h after the initial experiments (retrieval, see Fig 1). Rats were placed on the platform and the latency time necessary to enter the dark compartment was estimated. A cut-off time of 180 s was used. After completion of experiments, the placement of the cannula was verified (methylene blue staining of cryostat brain sections). To exclude effects of acidity of aluminum solutions, an additional experiment with acidified NaCl (pH 3.2) was performed. All data were statistically treated by the nonparametric *U*-test.

TABLE 1

TIME SCALE OF DRUG ADMINISTRATION DURING THE LEARNING EXPERIMENT

Group of Rats	0 h (Footshock)	22 h	23 h	24 h (1st Retention)
1		$AlCl_3$ ICV	NaCl ICV	
2		NaCl ICV	AVP ICV	
3		$AlCl_3$ ICV	AVP ICV	
4		NaCl ICV	NaCl IP	
5		$AlCl_3$ IP	NaCl IP	
6		NaCl IP	AVP IP	
7		$AlCl_3$ IP	AVP IP	
8		NaCl IP	NaCl IP	

The concentrations of the agents were $AlCl_3$ ICV: 200 μg in 5μl NaCl, IP: 20 mg in 0.5 ml NaCl; AVP, ICV: 10 ng in 5 μl NaCl, IP: 500 ng in 0.5 ml NaCl.

RESULTS

The behavioral data are summarized in Figs. 1 and 2. After ICV application of $AlCl_3$ alone, the avoidance latency was significantly decreased ($p = 0.05$). AVP alone increased the latency period ($p \leq 0.001$). When $AlCl_3$ and AVP were combined, the latency period was drastically reduced (much lower than $AlCl_3$ alone, $p \leq 0.001$).

Quite a different behavioral pattern was observed after IP administration. Immediately after injection of the metal solution the animals showed an expressed fighting behavior, which

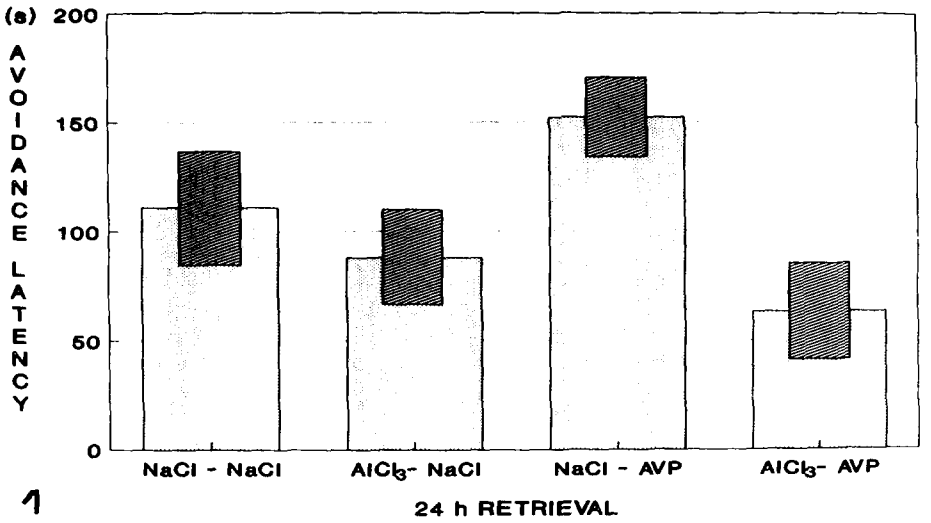

FIG. 1. Effect of ICV injection of aluminum, vasopressin, or a combination of both agents on the 24-h retrieval of a passive avoidance task in rats.

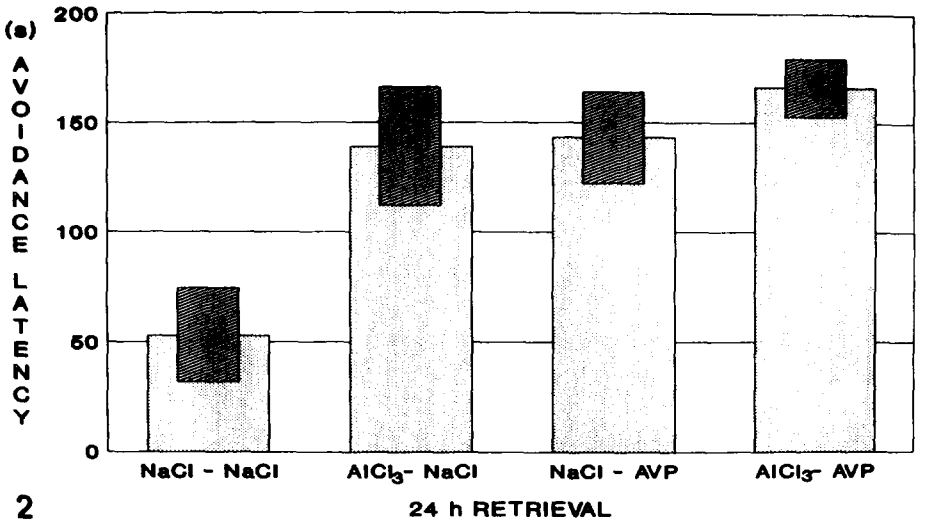

FIG. 2. Effect of IP infusion of aluminum, vasopressin, or a combination of both agents on the 24-h retrieval of a passive avoidance task in rats.

condisted of attacking one another. This phase of aggression lasted up to 40 min.

In the 24-h retention test Al-treated rats showed a prolonged avoidance latency compared to the saline controls ($p \leq 0.001$). AVP alone also enhanced the duration of latency ($p \leq 0.001$). Moreover, the combination of Al and AVP further prolonged latency time (though not significantly).

DISCUSSION

Aluminum is known to attenuate both learning and memory processes in animals and, most probably, in humans when it is repeatedly presented to the brain [for recent reviews, see (8,18,19)]. Less is known about neurotoxic effects of the metal after a single administration. There is evidence that ICV-applied aluminum rapidly crosses the blood-brain barrier (13) and changes the activities of choline acetyltransferase and acetylcholine esterase in the rat's hippocampus (7,13,18). Further, it has been reported that after injection of aluminum tartrate into the right lateral ventricle of rabbit pups there occurs a disruption of the retention of an active avoidance task (15). Our data demonstrate that a single ICV infusion of Al acutely influences memory storage in adult rats. Moreover, the neurotoxin seems to be able to remove AVP-evoked enhancement of the 24-h retention of a passive avoidance task. We take this result as a hint for a very fast action of the metal on the CNS. However, the mechanisms by which Al might do so are not clear at present because most of the known neurotoxic effects of the metal need much more time to develop [for review, see (8)].

Our preliminary (and currently highly speculative) explanation is that Al interacts with AVP at the behavioral level via a modulation of certain neurotransmitter systems [for example, the cholinergic (7,13,18)]. The finding that Al after IP injection prolongs the latency time in rats was rather unexpected. We tend to believe that this action of the metal has nothing to do with a better recall of the stored information, because an imrovement of learning and/or memory due to aluminum has never been observed. Instead, it is imaginable that the prolongation of the retention is an expression of an "unspecific" stress. Interestingly, AVP-evoked enhancement of retrieval is not blocked by Al, when both substances are given IP. Vasopressin does not belong to the group of peptides that gains better access to the brain under the influence of Al (3-5). Hence, the slight increase of latency time after combined application of AVP and aluminum cannot be explained as a result of increased AVP entry into the CNS. It cannot be excluded that IP injection of aluminum triggers yet unknown processes that finally lead to a release of vasopressin in the CNS. However, this intriguing idea remains to be proven in further studies. In summary, it can be stated that aluminum is apparently capable of altering rat learning behavior after a single presentation to the brain, and that the neurotoxin interacts with neuronally active peptides such as AVP in modulating rat behavior.

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REFERENCES

1. Ader, R.; Weijnen; J. A. W. M.; Moleman, P. Retention of passive avoidance response as a function of the intensity and duration of electric shock. Psychon. Sci. 26:125-128; 1972.
2. Alfrey, A. C.; Mishell, J. M.; Burks, S. R.; Contiguglia, I.; Rudolph, H.; Lewin, E.; Holmes, J. H. Syndrome of dyspraxia and multifocal seizures associated with chronic hemodialysis. Trans. Am. Soc. Artif. Intern. Organs 18:257-261; 1972.
3. Banks, W. A.; Kastin, A. J. Saturable transport of peptides across the blood-brain barrier. Life Sci. 41:1319-1338; 1987.
4. Banks, W. A.; Kastin, A. J. Aluminum-induced neurotoxicity: Alterations in membrane function at the blood-brain barrier. Neurosci. Biobehav. Rev. 13:47-53; 1989.
5. Bernstein, H.-G.; Stark, H.; Poeggel, G.; Schwarzberg, H.; Müller, M. Does aluminum alter peptide transport through the blood-

brain barrier? Testing a hypothesis. In: Elsner, N.; Richter, D. W., eds. Rhythmogenesis in neurons and networks. Stuttgart: Georg Thieme; 1992:602.
6. Bohus, B.; Urban, I.; von Wimersma Greidanus, T. J. B.; de Wied, D. Opposite effects of oxytocin and vasopressin on avoidance behaviour and hippocampal theta rhythm in the rats. Neuropharmacology 17:239–247; 1978.
7. Cherroret, G.; Bernuzzi, V.; Desor, D.; Hutin, M.-F.; Burnel, D.; Lehr, P. R. Effects of postnatal aluminum exposure on choline acetyltransferase activity and learning abilities in the rat. Neurotoxicol. Teratol. 14:259–264; 1992.
8. Hewitt, C. D.; Savory, J.; Wills, M. R. Aspects of aluminum toxicity. Clin. Toxicol. 10:403–422; 1990.
9. Klatzko, I.; Wisniewski, H.; Streicher, E. Experimental production of neurofibrillary degenration. I. Light microscopic observations. J. Neuropathol. Exp. Neurol. 24:187–197; 1965.
10. Kovacs, G. L.; Telegdy, G. Role of oxytocin in memory and amnesia. Pharmacol. Ther. 18:375–395; 1982.
11. Kruck, Th. P. A.; McLachlan, D. R. C. Aluminum as a pathogenic factor in senile dementia of Alzheimer type: Ion specific chelation. In: Alzheimer's disease and related disorders. New York: Alan R. Liss Inc; 1989:1155–1161.
12. Lipman, J. J.; Colowick, S. P.; Lawrence, P. L.; Aburad, N. N. Aluminum induced encephalopathy in the rat. Life Sci. 42:863–875; 1988.
13. Peng. J. H. F.; Xu, Z. X.; Parker, J. C.; Friedlander; E. R.; Tang, J. P.; Melethil, S. Aluminum-induced acute cholinergic neurotoxicity in rats. Mol. Chem. Neuropathol. 17:79–89; 1992.
14. Perl, D. P.; Brody, A. R. Alzheimer's disease: x-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. Science 208:297–299; 1980.
15. Petit, T. L.; Biederman, G. B.; Jonas, P.; Le Boutillier, J. C. Neurobehavioral development following aluminum administration in infant rabbits. Exp. Neurol. 88:640–651; 1985.
16. Schulz, H.; Kovacs, G. L.; Telegdy, G. Effect of physiological doses of vasopressin and oxytocin on avoidance and exploratory behaviour in rats. Acta Physiol. Acad. Sci. Hung. 45:211–215; 1974.
17. Schwarzberg, H.; Bernstein, H.-G.; Reiser, M.; Günther, O. Intracerebroventricular administration of insulin attenuates retrieval of a passive avoidance response in rats. Neuropeptides 13: 79–81; 1989.
18. Yates, C. M.; Simpson, J.; Russell, D.; Gordon, A. Cholinergic enzymes in neurofibrillary degeneration produced by aluminum. Brain Res. 197:269–274; 1980.
19. Yokel, R. A.; Provan, S. D.; Meyer, J. J.; Campbell, S. R. Aluminum intoxication and the victims of Alzheimer's disease: Similarities and differences. Neurotoxicology 9:429–442; 1988.