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Physiology & Behavior 83 (2005) 793–803

PHYSIOLOGY & BEHAVIOR

Enhanced zinc consumption causes memory deficits and increased brain levels of zinc

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Received 10 May 2004; received in revised form 21 September 2004; accepted 4 October 2004

Abstract

Zinc deficiency has been shown to impair cognitive functioning, but little work has been done on the effects of elevated zinc. This research examined the effect on memory of raising Sprague–Dawley rats on enhanced levels of zinc (10 ppm $ZnCO_3$; 0.153 mM) in the drinking water for periods of 3 or 9 months, both pre- and postnatally. Controls were raised on lab water. Memory was tested in a series of Morris Water Maze (MWM) experiments, and zinc-treated rats were found to have impairments in both reference and working memory. They were significantly slower to find a stationary platform and showed greater thigmotaxicity, a measure of anxiety. On a working memory task, where the platform was moved each day, zinc-treated animals had longer latencies over both trials and days, swam further from the platform, and showed greater thigmotaxicity. On trials using an Atlantis platform, which remained in one place but was lowered on probe trials, the zinc-treated animals had significantly fewer platform crossings, spent less time in the target quadrant, and did not swim as close to the platform position. They had significantly greater latency on nonprobe trials. Microprobe synchrotron X-ray fluorescence (μSXRF) confirmed that brain zinc levels were increased by adding $ZnCO_3$ to the drinking water. These data show that long-term dietary administration of zinc can lead to impairments in cognitive function.
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Keywords: Zinc; Cognitive deficits; Spatial memory; Morris Water Maze; Drinking water; Biometals; Synchrotron X-ray fluorescence; Brain concentrations of zinc; Rats; Learning; Thigmotaxicity; Atlantis platform; Working memory

1. Introduction

Zinc is the fourth most abundant intercellular metal and a biologically essential trace metal that is found in over 200 enzymes and proteins [1]. Within the central nervous system, zinc is found in high levels in the hippocampus, the amygdala, the striatum, and the neocortex. The highest levels are found in the hippocampus, particularly within the hilus and stratum lucidum region of CA3. Lower levels are found in the stratum radiatum and the stratum oriens of CA1 [2].

The adverse effects of zinc deficiency on physiology and behavior are well documented (for review, see Ref. [3]). Recently, attention has also focused on the possible adverse effects of elevated concentrations of zinc, which is known to play a major role in cell damage following stroke [4] and may be a risk factor in Alzheimer's disease [5–9]. Elevated zinc has been shown to have adverse gastrointestinal effects [10], but little work has been done on the effects on cognition. This is potentially a concern because zinc is the

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0031-9384/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2004.10.009

most abundant and the most soluble of the transition metals in natural systems [11], and levels of zinc in natural waters, especially in reservoir sediments, are continuing to rise while levels of other metals, such as lead, have fallen significantly [12].

Both natural and anthropogenic factors influence zinc levels in the environment. Environmental zinc levels are currently increasing as a result of increased industrial emissions and zinc's association with automobile materials. The current EPA standard for maximum contaminant levels of 5 mg/l solute zinc is based on the threshold for astringent taste, although zinc at these levels has been reported as toxic to fish and marine invertebrates [13]. Rats given short-term, high doses of zinc chloride (50 or 100 mg/kg by gavage at 10% of body weight) have been shown to have deficits in spatial learning [14]. Adverse effects on humans have been previously been reported at doses greater than 40 mg/l [15], and, more recently, cognitive deficits have been reported in infants given zinc supplements of 30 mg daily [16]. Because the blood–brain barrier acts to regulate the inflow of metals [17,18], it has been thought that excess zinc in the diet does not change the concentration in the brains of animals or humans unless they are zinc-deprived. Short-term dietary administration does not appear to change zinc levels [19].

There are three distinct pools of zinc in the brain: protein-bound zinc, free zinc, and vesicular zinc. Protein-bound zinc occurs in the structure of zinc-containing enzymes and accounts for 85–95% of all zinc in the brain. The levels of free zinc (Zn^{2+}) that exists in the cytosol or interstitial fluid, where it may serve as a neural signal in much the same manner as calcium, are thought to be low [20]. Vesicular zinc makes up no more than 5–15% of zinc in the brain and is colocalized in vesicles with glutamate. All zinc-containing neurons are glutamatergic, although only some glutamatergic neurons contain zinc [21]. Zinc acts as a neuromodulator and can inhibit GABAergic synapses [22]. It enhances conduction at AMPA receptors but inhibits conduction at NMDA receptors [22,23]. The enhanced conduction at AMPA receptors is a possible mechanism by which zinc induces neuronal cell death [4,24]. Inhibition of NMDA receptors has been shown to impair spatial memory in rats and mice [25–28].

Vesicular zinc is stained histochemically by the Timms–Danscher sulphide silver stain [29] and the TSQ fluorescence stain [2], but this stain does not detect enzymatic zinc. Spatially resolved synchrotron X-ray fluorescence can be used to measure total zinc and the distributions of other elements in complex matrices [30,31]. This method consists of exciting the specimen with an intense X-ray beam from a synchrotron source and measuring the energies and intensities of emitted fluorescent X-rays. For biological materials, the X-ray microprobe offers distinct advantages over other analytical techniques by allowing analyses to be done in situ with little or no chemical pretreatment. The technique also provides low detection limits (1 ppm or better) with spatial resolutions on the order of 10 μm. Both vesicular and bound zinc are detected.

To evaluate the potential health risks associated with increasing levels of zinc in drinking water, we sought to examine whether long-term ingestion of low levels of zinc would affect behavior and brain levels of zinc. We have examined spatial memory in rats raised both pre- and postnatally on $ZnCO_3$-enhanced water in three separate experiments using the Morris Water Maze (MWM), which has been used extensively to examine spatial memory in rats [32–35]. We also compared the brain levels of zinc in 9-month animals raised either on normal or $ZnCO_3$-enhanced water using microbeam synchrotron X-ray fluorescence (μSXRF) analysis. In this research, we show that long-term administration of $ZnCO_3$ in drinking water can impair spatial memory and change brain levels of zinc. Partial results of this experiment have been previously reported at the Society for Neuroscience annual meetings.

2. Methods

Sprague–Dawley rats were maintained on water containing enhanced levels of zinc in three separate experiments using the Morris Water Maze (MWM), as described in detail below. In Experiment 1, the MWM platform remained in the same position throughout the experiment. This method is considered to be a test of reference memory [35], which was also measured in Experiment 2, part 1. A visible platform was used for 1 day at the end of Experiments 1 and 2, part 1, and Experiment 3 to examine cued memory. Working memory was examined in Experiment 2, part 2, as the platform was moved each day [36]. Experiment 3 used an "Atlantis" platform, which was submerged on every sixth trial and remained in the same position throughout the experiment to more carefully examine the spatial aspects of the reference memory task [37,38]. An HVS computerized system was used to collect MWM data in Experiments 2 and 3.

This experiment was approved by the George Mason University animal subjects committee, and rats were cared for and maintained in accordance with the Federal and University guidelines.

2.1. Water preparation/zinc consumption

Zinc-enhanced water, as 10 ppm (0.153 mM) $ZnCO_3$, was prepared at the United States Geological Survey (USGS), Reston, VA. Average laboratory water pH was 7.7, and the average pH of $ZnCO_3$-enhanced water was 7.8. Laboratory tap water was analyzed using inductively coupled plasma-optical emission spectroscopy and ion chromatography at least twice yearly for a suite of anions (Cl, SO_4, NO_3) and cations (Zn, Fe, Cu, Ca, Mn). The mean zinc concentration in laboratory tap water was 0.02 ± 0.005 ppm.

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