

Early exposure to manganese causes attention deficits in rats

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Environmental toxicologist Donald Smith has been studying the neurological effects of excess manganese for over 15 years. Credit: Carolyn Lagattuta

Researchers using a rodent model of childhood manganese exposure have found that too much manganese early in development causes lasting attention deficits and other impairments.

Manganese is an essential element, required by the body in trace amounts. High levels of exposure can have neurotoxic effects, however, leading to a condition called "manganism" in adults exposed to manganese dust or fumes in mining, welding, and other industrial occupations.

Studies of children and adolescents have associated excess manganese in the diet with <u>attention deficits</u>, but confounding factors in those studies have made it impossible to show a cause and effect relationship. Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurobehavioral disorder in children, but its cause remains unclear and probably involves many different factors.

The new study, published in *Environmental Health Perspectives*, is the first study to establish a causal link between exposure to elevated manganese in the diet and attentional dysfunction in an animal model, according to senior author Donald Smith, professor of environmental toxicology at UC Santa Cruz.

"There are many environmental and biological factors that have been associated with increased risk for attention deficits in children, so it's very challenging to understand which factors may actually contribute to



or cause attention deficits," Smith said. "Our study clarifies the effects of a single environmental agent, and it allowed us to tease out the specific nature of the deficits it causes, which is extremely difficult if not impossible to do in human studies."

The most common source of exposure to excess manganese is drinking water from wells, because groundwater in some areas is naturally high in manganese. Soy-based infant formulas also have much higher levels of manganese than breast milk. The exposure levels used in the rat study were chosen to produce increases in manganese intake (relative to the normal intake of baby rats) comparable to the relative increases that would be experienced by infants and young children exposed to contaminated drinking water, soy-based formulas, or both.

The impairments seen in the exposed rats were comparable in magnitude to the attentional dysfunction seen in children with ADHD, Smith said. A previous study by Smith's lab found that manganese exposure also causes deficits in fine motor abilities in rats, and he noted that similar deficits in coordination and dexterity are often seen in children with ADHD.

In the new study, newborn rats were exposed to 0, 25, or 50 milligrams of manganese per kilogram of body weight per day, for either the first 21 days after birth or for the duration of the study (about six months). Behavioral testing for attention and impulsivity began when the rats were about 80 days old and continued six days a week for three months, using a well-accepted protocol. The animals were trained to focus their visual attention on a wall in the testing chamber with five ports and to respond to a brief flash of light within one port by poking their nose into that port. The researchers introduced distractions by delivering a puff of scented air into a different port within the test chamber.

"The odor-based distractor is very hard for the animals to ignore because



they have very strong olfactory senses," Smith said. "With thousands of response trials over months of testing, we were able to obtain very detailed information to assess specific functions that we can compare to the assessments used for children."

The impairment caused by manganese exposure was most pronounced in the area of selective attention, assessed by response accuracy in the presence of a distracting odor. Deficits were also seen in other areas related to attention, but manganese exposure did not affect impulse control.

The results also showed that the susceptibility to manganese changed as the animals grew and matured. They were particularly sensitive to the neurotoxic effects during the early postnatal period, before weaning. According to Smith, the dependence of toxicity on the dose as well as the timing and duration of exposure is complicated for a substance like manganese that also has a beneficial biological function.

"The typical dose-response curve for biologically essential elements is Ushaped: too little is bad, too much is bad, and you want to be somewhere in the middle. This study shows that vulnerability also changes over the course of neurodevelopment," he explained.

In the experiment, the rats got a constant dose relative to their body weight, but their sensitivity to it changed as they aged. At the lower dose level (25 mg/kg/d), animals exposed throughout the study actually showed less impairment than those exposed only during the early postnatal period. At the higher dose level, the level of impairment from the longer exposure was the same as the effects of the early life exposure.

"The lower dose exposure over the early life period produced lasting deficits in attention, but if that same dose was continued into adulthood,



it helped lessen the deficits caused by the earlier exposure. At the higher dose, however, they were unable to recover," Smith said.

He noted that such complex responses to differences in dose, timing, and duration of exposure may underlie the inconsistencies in published studies of the relationship between blood levels of <u>manganese</u> in humans and neurobehavioral deficits.

"It's difficult if not impossible to reconstruct the exposure histories of children," Smith said. "If we knew their <u>exposure</u> histories more thoroughly, we would likely find stronger associations with the neurobehavioral deficits."

More information: Stephane A. Beaudin et al, Early Postnatal Manganese Exposure Causes Lasting Impairment of Selective and Focused Attention and Arousal Regulation in Adult Rats, *Environmental Health Perspectives* (2016). DOI: 10.1289/EHP258

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