STATEMENT

Synopsis of Research Report 119

HEALTH EFFECTS INSTITUTE

Manganese Transport at the Blood–Brain Barrier

Metals comprise a large group of elements. Many of these metals are essential to living systems because they participate in a variety of biological functions, but they can be toxic at concentrations above those needed in the body. Exposure to some metals has been found to cause neurologic damage—for instance, in children exposed to low levels of lead via ingestion and in workers exposed to moderate to high levels of manganese via inhalation. Metals are present as particles or particle components in emissions from vehicles and other sources and have been implicated as one possible reason for the adverse health effects associated with airborne particulate matter exposure.

As part of its research program to address the possible health effects of metal emissions from motor vehicles and fuels, an HEI workshop held in February 1998 focused in part on fuel additives containing cerium, iron, and manganese. One such additive, methylcyclopentadienyl manganese tricarbonyl (MMT), is an antiknock agent that also reduces emissions of nitrogen oxides. Because MMT contains manganese, controversy exists about whether its widespread use as a fuel additive may pose a health risk to the general population. MMT is currently used in Canada and parts of the United States. Pending completion of a mandated series of emissions and toxicity tests in 2004, the US Environmental Protection Agency will determine whether regulation of MMT as a fuel additive is necessary.

After the 1998 workshop, HEI issued a Request for Preliminary Applications, RFPA 98-4, *Research on Metals Emitted by Motor Vehicles*. In response, Dr Robert Yokel proposed to study the mechanisms by which manganese enters and leaves the brain across the blood–brain barrier and, in particular, whether transporter molecules are involved. The blood–brain barrier is a function of the walls of small blood vessels that shield the brain from possibly harmful molecules. Certain molecules may cross the blood–brain barrier via diffusion or via carrier-mediated transport. HEI funded Dr Yokel's study in part because it would be the first direct investigation of whether specific transporter molecules remove manganese from the brain. Evidence for carrier-mediated transport of manganese out of the brain would be particularly interesting in that it would indicate a possible mechanism for preventing manganese accumulation, thereby affecting the likelihood of neurologic damage from chronic low-level exposure.

APPROACH

In this study Drs Yokel and Crossgrove used in vivo brain perfusion in rats as well as in vitro tests in several cell lines to assess specific characteristics of manganese transport, such as pH and energy dependence. Manganese transport rates were compared with those of sucrose and dextran, which do not easily cross the blood–brain barrier. Experiments to identify putative transporters focused on known transport molecules, such as a divalent metal transporter, a monocarboxylate transporter, and calcium channels. The investigators used both a genetic approach (comparing results in rats with and without a functional divalent metal transporter) and a pharmacologic approach (evaluating manganese transport function in the presence of several selective inhibitors).

RESULTS AND INTERPRETATION

Yokel and Crossgrove have provided convincing evidence that manganese enters the brain via carrier-mediated transport, confirming and extending previous observations. They also are the first to have shown that manganese leaves the brain via diffusion only, a much slower process than carrier-mediated transport. Experiments conducted to identify the transporters involved in manganese uptake into the brain suggested that the divalent metal transporter DMT-1, which is specific for iron uptake, is not involved. However, the identity of the putative manganese transporters remains elusive.

Continued

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Drs Robert A Yokel and Janelle S Crossgrove at the University of Kentucky Medical Center, Lexington KY. The complete report, *Manganese Toxicokinetics at the Blood–Brain Barrier*, can be obtained from HEI or our website (see reverse side). YOKEL 119

The finding that manganese transport out of the brain occurs via the slow process of diffusion, rather than via carrier-mediated transport, is important: it suggests that no mechanism exists to protect the brain from accumulating manganese. This finding has important implications for neurotoxicity resulting from chronic manganese exposure. Although Yokel and Crossgrove studied manganese transport rates in rats, their observations may be relevant to humans because transport mechanisms at the blood–brain barrier are similar in rodents and humans. Their results support the current understanding that the potential for manganese accumulation in the brain should be considered when assessing risk from exposure to manganese in the environment. Future studies and risk assessments should also consider susceptible populations (such as people with iron deficiencies or liver disease) who may be at greater risk from increased manganese uptake. New research would be useful to confirm the lack of a carrier-mediated transport system for removing manganese from the brain and to address the relevance of these findings to humans.

Manganese Toxicokinetics at the Blood–Brain Barrier

Robert A Yokel and Janelle S Crossgrove

HEI STATEMENT

INVESTIGATORS' REPORT

COMMENTARY Health Review Committee

HEALTH EFFECTS INSTITUTE

Charlestown Navy Yard
120 Second Avenue
Boston MA 02129-4533 USA

+1-617-886-9330
+1-617-886-9335 fax

pubs@healtheffects.org
www.healtheffects.org

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