The Role of Manganese in Human Disease*

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ABSTRACT

The role of manganese in the human body as well as its toxic effects as a potent neurotoxic metal are discussed. At present, emphasis is being placed on the study of susceptibility to manganese poisoning because manganese is a potential atmospheric pollutant, if lead in gasoline is to be replaced by Mn. Mn is a potent antiknock agent. Anemic individuals who show increased iron and manganese intestinal absorption and newborns might be among the susceptible populations.

Introduction

Manganese (Mn) is an essential oligoelement.1,8,16 It is the fourth most abundant biological trace element in the earth's crust, although its concentrations in mammal tissues are extremely minute (1 to 2 ng per ml of human serum).2 Food is the main source of Mn in humans with a daily intake of approximately three mg. However, the intestinal absorption in adult man is no more than 3 percent. Furthermore, after rapid excretion by the liver, a net amount of 1 percent is retained.2 This amounts to a net retention of approximately 30 μg per day. Most inhaled Mn (60 to 70 percent8) is deglutted and eventually absorbed in the intestines, the percent depending largely upon particle size.8,11,12 Absorbed Mn concentrates rapidly10 in organs rich in mitochondria to which it attaches, i.e., liver, pituitary, pancreas.8 Homeostasis is regulated by the liver, and excesses of the metal are readily excreted into the bile.5,15

Normal individuals excrete 54Mn from the body with a half-life of 37 days ±, whereas miners, overexposed to inhalation of ore dust (air concentration of 55Mn > 5 mg per m³) excrete 54Mn with a half-life of 15 days ± 2.2 The respective whole blood 54Mn concentrations were 11 ng per ml ± 1.1 and 25 ng per ml ± 1.6, p < 0.001.

The entrance of Mn into the brain is a slow process. In normal rats, it reaches a maximum of 1 percent of intraperitoneally injected 54Mn after 30 days, followed by a slow clearance with a half-life of 150 days.

Manganese Poisoning

Chronic Mn poisoning is a severe industrial disease affecting miners and workers
in manganese mills and foundries. It occurs most frequently in the manganese mining villages of Russia, India, North Africa, Yugoslavia, Cuba, Chile, etc.10 The estimated incidence is as high as 25 percent of the exposed population in some areas and as low as 2 to 4 percent in Chile. It occurs after variable periods of inhalation of ore dust.

A psychotic period at the onset of the disease consistently appears in all cases in Chile, but is notably absent in reports from steel foundries and ore crushing plants in the United States.4 This period, referred to by the villagers as "manganic madness," is characterized by hallucinations, delusions and compulsions. In most cases, the patients are subsequently aware of the abnormal nature of these phenomena. The psychosis lasts from one to three months whether or not the patients are immediately removed from the mines.10 Toward the end of the psychotic period or immediately thereafter, neurological symptoms characteristic of extrapyramidal involvement emerge. In the Chilean patients, these symptoms included loss of facial expression, rigidity, slowness of movements (bradykinesia), diminution of postural reflexes, and impairment of speech. A few patients developed a dystonia musculorum deformans. In one study of U.S. workers in a crushing plant, rigidity was notably absent; bradykinesia and impairment of balance were predominant.4

**Background for Treatment**

The successful treatment of Wilson's disease with metal-binding agents seemed to provide a precedent for treating chronic manganese poisoning since the two diseases presented certain clinical similarities. The rationale for this approach was weakened when excesses of Mn were found in the tissues of healthy, exposed Mn miners, whereas central nervous system (CNS)-damaged ex-miners, who were no longer exposed, had cleared these loads. The brain damage appeared to be caused by flooding with Mn, but the symptoms persisted after such flooding had been terminated. Even when parts of the brain still contained an excess of Mn, the metal was apparently in a tightly sequestered state. It would appear, therefore, that the brain suffered a structural injury due to Mn.

**Similarity to Parkinsonism**

Mn poisoning has many features in common with Parkinson's disease,10 in which structural damage to the brain is marked by diminished melanin in the substantia nigra. Metabolic changes consist of diminished catecholamines and serotonin in the corpus striatum. These metabolic features have been duplicated in experimental Mn poisoning.13 The function of melamins is still unknown, but the biogenic amines are neurotransmitters. Upon systemic administration, these amines are bound or inactivated in the periphery and are prevented from entering the brain. Therefore, inactive precursors must be administered from which they can be synthesized by the brain. A common precursor of both melanin and catecholamines is the amino acid 3,4-dihydroxyphenylalanine (dopa). The administration of L-dopa to Parkinsonian patients produced significant improvement, regardless of the cause of the disease. This suggests that the metabolic sequelae were related to the localization (not to the nature) of the brain damage.

Although the pathology of chronic Mn poisoning has not yet been sufficiently studied, it has been speculated that at least some of the symptoms common to the two diseases might be due to similar metabolic sequelae within surviving neurons. In Parkinson's disease, slowly increasing doses of levodopa have produced marked improvement of rigidity and bradykinesia, and high doses have decreased or stopped tremor. During treatment, some previously
bradykinetic patients have developed involuntary movements. Other side effects have been the emergence of mental aberrations and intermittent loss of the therapeutic action of levodopa.

**Response to Levodopa**

In manganic patients, the response to levodopa has been a function of the neurological pattern of symptoms. Rigid, bradykinetic patients with loss of postural reflexes and impairment of gait have responded to doses greater than three g per day, with marked to total reduction of rigidity, improvement of postural reflexes and gait, and correction of bradykinesia. However, no improvement of speech was noted. The therapeutic effects lasted during the time levodopa was administered (for periods up to four years), but the symptoms re-emerged after seven to 10 days on placebo therapy. Notably absent in these patients have been side effects such as involuntary movements, mental aberrations, or intermittent loss of therapeutic effect. Several of these patients returned to minor, menial jobs.

A second type, dystonic manganic patients, showed improvement of dystonia and diminution of passive muscular tonus on doses of 4 to 5 g of levodopa per day. However, physical strain and emotional stress can trigger the appearance of dystonic crisis. After periods of three to four months, levodopa lost its effectiveness, and dystonia re-emerged with greater intensity than the pretreatment level. Placebo administration for 10 to 30 days caused this abnormality to regress, and levodopa therapy was re instituted with the same therapeutic effects as before.

A third type was represented by one patient without rigidity, but presenting muscular hypotonus, tremor, slowness and impaired postural reflexes. Treatment with 1.2 g of levodopa per day produced a marked aggravation of hypotonia, impairment of postural reflexes, and further impairment of gait; three g per day also caused worsening of tremor. Placebo administration restored pretreatment levels after 48 hours.

In the U.S., Rosenstock has reported that levodopa, administered to a patient working in a steel foundry, improved a mask-like face, markedly improved slowness, but did not improve dystonia. Greenhouse has reported, in four patients from a Mn ore crushing plant, a clinical pattern of impairment of postural reflexes and slowness of movement, but without major extrapyramidal symptoms such as rigidity, tremor, etc. These patients did not respond to doses of five g of levodopa per day. This investigator has not reported major side effects with levodopa treatment.

**Susceptibility to Mn Poisoning**

It has previously been stated that the estimated incidence of manganism varies between 25 percent to 4 percent of the exposed population, occurring after variable periods of exposure to inhalation of ore dust (6 months to 24 years). Possible individual susceptibility has been related to variations of intestinal absorption of Mn. Individuals with increased iron absorption have increased Mn absorption as well. Absorption of Mn in normals is 3 percent ± 0.5; in anemic patients the rate is 7.5 percent ± 2. Fe absorption was 11 percent ± 10, and 64 percent ± 22, respectively. Information on intestinal absorption of Mn in infants is not available.

In iron deficient rats, plasma binding capacity of Mn (transferrin) is increased approximately 100 percent, as is the entrance of Mn into the brain as shown in figure 1. This appears coupled with transport of Mn to the blood brain barrier by transferrin and would link, therefore, increased Mn binding capacity to increased entrance of Mn to the CNS. Newborn and infant rats, compared with adult rats,
had a four-fold increased entrance of $^{54}\text{Mn}$ into the brain, which would indicate immaturity of the blood brain barrier at these early ages.

**Manganese as an atmospheric pollutant and new industrial hazard**

Our knowledge of the effects of overexposure to Mn on humans is limited to observations made on miners and industrial workers. Mn is inhaled in mines and foundries. The present maximum permissible amounts of Mn in air for these workers, established for a 40-hour-work week, is 5 mg per m$^3$ in the U.S., and 0.3 mg per m$^3$ in USSR. The maximum permissible dose of Mn in the air for pregnant women, infants and children in constant exposure is not known. However, this information is vitally necessary if lead in gasoline and fuel oil is replaced by methyl Mn tricarbonyl compounds.

A crude estimate can be made of the consequences of increasing Mn in the air. Exactly 0.5 g of Mn per gallon of gasoline would increase the level of Mn in the atmosphere from approximately 0.05 $\mu$g per m$^3$ to 0.2 to 0.8 $\mu$g per m$^3$. As a result, the current inhalation of 2 $\mu$g per day by an adult man would be increased to 6 to 24 $\mu$g per day, assuming an inhalation by the adult of 30 m$^3$ per day. The normal net retention from alimentary Mn is approximately 30 $\mu$g of Mn per day. Lesser amounts of Mn added to gasoline would reduce the amount of Mn per m$^3$ proportionately. Although the final disposition of these forms of inhaled Mn has not been fully determined, it appears probable that most of the Mn inhaled eventually would be deglutted and absorbed proportionately by the intestine.

The maximal inhalation of Mn from gasoline appears to be in the range of the daily normal adult absorption. However, iron deficient patients absorb currently more Mn. The consequences of this increased absorption are acceleration of Mn total body turnover and increased erythrocyte $^{55}$Mn concentration. No clinical consequences have been defined, and the entrance of $^{54}$Mn into the brain has not yet been assessed. As stated, $^{54}$Mn entrance into the brain of the iron deficient rat is enhanced.

The adult population appears to be protected from Mn by two barriers: the intestinal barrier and the blood brain barrier. However, the fetus, newborn and young infants are probably not protected in the same manner. For this group, the comparison intake-inhalation does not appear valid. Milk is a Mn deficient diet. Concentration of Mn in milk is 0.14 $\mu$g per g, and the daily intake of Mn is 140 to 200 $\mu$g. Therefore, inhalation of environmental Mn could markedly increase the body burden.
of Mn. In the young rat, intestinal absorption is of the order of 70 percent compared to 1 to 2 percent in the adult. The entrance of $^{54}$Mn into the brain of the young rat is also increased four-fold versus the adult rat.

These arguments justify the inclusion of newborns and infants among the potentially susceptible population, and underline the need to clarify their situation.

Summary

Manganese is a potent neurotoxic metal. Whereas the normal adult population appears to be protected by the intestinal and blood brain barriers, this is not the case in Fe deficient patients and most likely in newborn and infants.

References