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MANGANESE POISONING:
A METABOLIC DISEASE OF THE BRAIN

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A METABOLIC DISEASE OF THE BRAIN*

Manganese is a potent neurotoxin to industrial workers. It is also emerging as a potential environmental pollutant if it is to replace lead in gasoline. Thus the studies performed in Chilean miners during the last 10 years might become relevant to the general population. Manganese has induced psychosis followed by nonprogressive extrapyramidal damage in the central nervous system of workers. In parallel studies with Parkinson's disease, we have demonstrated that in both disorders the injury to the central nervous system consists in a diminution of synthesis of the neurotransmitter dopamine, which can be restored by overloading the central nervous system with the precursor amino acid, levodopa. Furthermore, susceptible populations i.e., individuals with iron deficiency and possibly newborns and infants, have been found to have an increased intestinal absorption of manganese. We, therefore, consider that future work concerning the effect of manganese on the central nervous system should concentrate on the definition of potentially susceptible populations and on the development of means of protection.

Background

Manganese (Mn) is an essential oligo element. It is the fourth most abundant biologic trace element in the earth's crust, although its concentrations in mammal tissues are extremely minute (1-2 ng/ml of human serum). Food is the main Mn source in humans with a daily intake of approximately 3 mg. The intestinal absorption in the adult man is, however, no more than 3 percent. Furthermore, after rapid liver excretion, only

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1 percent is retained. This amounts to a net retention of approximately 30 μg per day. Most inhaled Mn (60-70 percent) is swallowed and eventually absorbed in the intestine, in a percentage depending largely upon particle size. Absorbed Mn concentrates rapidly in organs rich in mitochondria to which it attaches itself, i.e., liver, pituitary, pancreas. Homeostasis is regulated by the liver, and excesses of the metal are readily excreted into the bile.

Normal individuals excrete Mn from the body with a half-life of 37 days ± 7, whereas miners, overexposed to inhalation of ore dust (air-concentration of Mn > 5 mg/m³), excrete Mn with a half-life of 15 days ± 2. The respective whole blood Mn concentrations are 11 ng/ml ± 1.1 and 25 ng/ml ± 1.6 p < 0.001.

The entrance of Mn into the brain is a slow process. In normal rats manganese concentration in the brain reaches a maximum of 1 percent, 30 days after intraperitoneal injections of Mn. Clearance is slow, with a half-life of 150 days.

Manganese poisoning

Chronic Mn poisoning is a severe industrial disease affecting manganese miners and workers in manganese mills and foundries. It occurs most frequently in the manganese mining villages of Russia, India, North Africa, Yugoslavia, Cuba, and Chile. 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. Poisoning happens after variable periods of inhalation of ore dust.

A psychotic period at the onset of the disease consistently appeared in all cases in Chile, but was notably absent in reports from steel foundries and ore crushing plants in the United States. This period, referred to by the villagers as "manganic madness," is characterized by hallucinations, delusions, and compulsions. In most cases, patients are subsequently aware of the abnormal nature of these phenomena. The psychosis lasts from 1 to 3 months whether the patients are
immediately removed from the mines or not. Toward the end of the psychotic period or immediately thereafter, neurologic symptoms characteristic of extrapyramidal involvement emerges. 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 similar to the spontaneously occurring dystonia musculorum deformans. In one study of U.S. workers in a crushing plant, rigidity was absent, but bradykinesia and impairment of balance were predominant.

**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 manganese were found in the tissues of healthy, exposed Mn miners, whereas CNS-damaged ex-miners, who were no longer exposed, had cleared these loads. The brain damage appeared to be caused by Mn flooding, 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 caused by Mn.

**Similarity to parkinsonism**

Mn poisoning has many features in common with Parkinson's disease, 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 replicated in experimental Mn poisoning. The role of melanin 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
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 a 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 caused by similar metabolic sequelae within surviving neurons. In Parkinson's disease, slowly increasing doses of levodopa have markedly improved 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.17/

Response to levodopa

In manganic patients the response to levodopa has been a function of the neurologic pattern of symptoms. Rigid, bradykinetic patients with loss of postural reflexes and impairment of gait have responded to doses greater than 3 g/day, with marked-to-total reduction of rigidity, improvement of postural reflexes and gait, and correction of bradykinesia. No improvement of speech9/ was noted, however. Therapeutic effects lasted the time of administration of levodopa (for periods up to 4 years), but symptoms reemerged after 7 to 10 days on placebo therapy. These patients suffered no side effects such as involuntary movements, mental aberrations, or intermittent loss of therapeutic effect. Several of them returned to minor, menial jobs.

A second type of patients, the dystonic manganics, showed improvement of dystonia and diminution of passive muscular tonus on doses of 4-5 g of levodopa per day. Physical strain and emotional stress may, however, trigger the appearance of a dystonic crisis. After periods of 3 to 4
months, levodopa lost its effectiveness, and dystonia reemerged with greater intensity than the pretreatment level. Placebo administration for 10 to 30 days caused this abnormality to regress, and levodopa therapy was reinstituted 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; 3 g per day also caused worsening of tremor. Placebo administration restored pretreatment levels after 48 hours.

In the United States, Rosenstock has reported that levodopa, administered to a patient working in a steel foundry, improved his mask-like face, markedly improved rigidity, slightly 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 or tremor. These patients did not respond to doses of 5 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 from between 4 percent to 25 percent of the exposed population, and that manganism occurs after variable periods of exposure to inhalation of ore dust (6 months - 24 years). Individual susceptibility may possibly be related to variations of intestinal absorption of Mn. Individuals with increased iron absorption have increased Mn absorption as well. Absorption of 54Mn in healthy persons is 3 percent ± 0.5; in anemic patients the rate is 7.5 percent ± 2. 54Fe 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, Mn plasma binding capacity (transferrin) is increased approximately 100 percent, as is the entrance of Mn into the brain. 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 $^{54}$Mn to the CNS. Newborn and infant rats, compared with adult rats, had a fourfold increased entrance of $^{54}$Mn into the brain, which would indicate immaturity of the blood brain barrier at these early ages.

During therapeutic attempts with levodopa, clinical and metabolic similarities and dissimilarities between Parkinson's disease and manganese poisoning emerged. In an effort to understand the nature of extrapyramidal disorders induced by manganese, these parallel studies were continued in the following areas: (1) influence of protein intake in the 'off-on' phenomenon in parkinsonian and manganic patients, and (2) correlation of electroencephalographic pattern during sleep in parkinsonian and manganic patients.

Protein intake and intermittent refractoriness to levodopa

We have identified a metabolic difference between patients with Parkinson's disease and those with manganese poisoning. Though high-protein intake enhances the intermittent refractoriness to levodopa (off-on phenomenon) in unstable parkinsonian patients, this has not been observed in manganic patients. In eight parkinsonian patients at Brookhaven, morning motor function scores were impaired from 26 ± 2 to 40 ± 3 (normalcy: 0; maximal impairment: 100, p<0.001). On high-protein diet (2 g/kg) the morning Parkinson's scores of these same patients, on the same amount of levodopa, were impaired from 26 ± 3 to 54 ± 3, p<0.0001. A low-protein diet (10 g of protein per day), achieved, however, a stability of motor function with morning scores between 25 ± 3 and 3:00 pm scores 24 ± 4, p<0.9. These effects of protein intake were blocked when a peripheral decarboxylase inhibitor MK-486 was used. In five manganic patients similar dietary maneuvers failed to produce morning or afternoon changes in the response to levodopa.
Furthermore, measurements of total body decarboxylation of levodopa $^{14}$C, showed no significant differences between parkinsonian and manganic patients with and without the peripheral decarboxylase inhibitor MK-486. In 14 Parkinson's disease patients, the $^{14}$CO$_2$ recovery per hour was 10.3 percent ± 0.69 (mean and SEM) and in 9 parkinsonian patients who received also MK-486, 4.5 percent ± 0.4, p<0.001. In seven manganic patients, injection of levodopa was followed by a $^{14}$CO$_2$ recovery of 9.9 percent ± 0.9 per hour, not statistically different from the parkinsonian patients and a reduction to 5.1 percent ± 1.08 while on MK-486, p<0.01. Six healthy manganese miners showed a decarboxylation of 16.2 percent ± 1.0 per hour and a reduction to 8.5 percent ± 1.4 on MK-486, p<0.01. Decarboxylation of L-tyrosine labeled with C14 in the carboxyl group, shows similar decarboxylation rate in parkinsonian, manganic, healthy miners, and controls, giving 7 percent ± 0.6; 6 percent ± 0.5 and 5 percent ± 0.3, respectively. No statistical diminution of decarboxylation of L-tyrosine was observed in neither of these groups on MK-486.

**Electroencephalographic changes in manganese poisoning**

Continuous electroencephalographic and myographic records were gathered during the hours of sleep, for two consecutive nights, in 10 healthy controls and 7 patients with manganese poisoning. Manganic patients were studied while off levodopa at basal clinical level and while on levodopa at optimal control. Significant changes in the distribution of rapid eye movement (REM) sleep were observed in these two groups. The fraction of sleep represented by REM was 13.9 ± 1.7 percent, p<0.02 in the controls and only 5.5 ± 0.6 percent, p<0.001 in the manganic patients off levodopa. The same manganic patients on optimal doses of levodopa had an increased REM period of 8.9 ± 0.7 percent, p<0.001. Samples of growth hormone analysis were gathered during the sleep period. Controls had a mean concentration of 4.95 ± 1.4 ng/ml of growth hormone while off levodopa and 1.64 ± 5, while on levodopa, p<0.05.

In summary, similarities between parkinsonism and manganese poisoning consist of marked correction of extrapyramidal symptoms and
signs and of a marked diminution of REM sleep that is partially corrected by levodopa. Dissimilarities consist of absence of levodopa-induced dyskinesia and of mental aberrations in patients with manganese poisoning. Furthermore, high-protein intake does not impair levodopa effects in manganic patients but does markedly so in unstable parkinsonian patients.

Manganese intake and catecholamine concentration in the brain of pregnant rats and newborns

Teratologic studies on the effects of levodopa were previously reported on, showing a protective effect of manganese in the induction of brown fat hemorrhage in the newborn. It was postulated that this effect was mediated by changes in the metabolism of catecholamines. A study of the possible changes in concentration of catecholamines in the brain while manipulating the intake of manganese was, therefore, undertaken. Pregnant rats were placed on a Hurley diet (exclusively manganese deficient) to which different concentrations of manganese during the entire period of pregnancy were added. After delivery, the level of dopamine in the brains of mothers on manganese-deficient diet was significantly decreased, 528 ± 59 ng/brain, as opposed to 848 ± 87 ng/brain, p<0.05, for mothers on a normal diet. Brain concentrations of noradrenaline in manganese-deficient rats showed a similar decrease, 198 ± 31 ng/brain, p<0.001, as opposed to 484 ± 42 ng/brain for rats on a normal diet. In the offsprings of these rats, dopamine brain concentrations were 38 ± 2 ng/brain and 51 ± 6 ng/brain respectively following manganese-deficient and normal manganese diets of the mothers. Norepinephrine concentrations on the brains of offspring were diminished following the manganese deficient diet.

Summary

We have presented information that shows manganese as a potent neurotoxic agent for industrial workers. We have demonstrated that the damage of the extrapyramidal system consists mostly in an impairment of the synthesis of the neurotransmitter dopamine that can be reversed by daily administration of the precursor, amino acid levodopa. We have linked susceptibility to
manganese poisoning to excessive absorption of the metal in patients with iron deficient anemia and have postulated that a potential susceptible group might be newborns and infants. In them, both the intestinal and the blood brain barrier are not fully developed. Therefore, if lead is to be replaced in gasoline by manganese, this metal will become a new environmental pollutant and toxicologic studies have to consider these potentially susceptible populations. Our work with the Chilean manganese miners would then become relevant to the general population.
REFERENCES


