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# EFFECTS OF MANGANESE ON THYROID HORMONE HOMEOSTASIS:

## POTENTIAL LINKS

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## Abstract

Manganese (Mn) is an essential trace nutrient that is potentially toxic at high levels of exposure. As a constituent of numerous enzymes and a cofactor, manganese plays an important role in a number of physiologic processes in mammals. The manganese-containing enzyme, manganese superoxide dismutase (Mn-SOD), is the principal antioxidant enzyme which neutralizes the toxic effects of reactive oxygen species. Other manganese-containing enzymes include oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases and glutamine synthetase. Environmental or occupational exposure to high levels of manganese can cause a neuropathy resembling idiopathic Parkinson's disease, commonly referred to as manganism. Manganism and Parkinson's disease are both characterized by motor deficits and damage to nuclei of the basal ganglia, particularly the substantia nigra, with altered dopamine (and its metabolites) contributing to these disorders. Dopamine, a major neurotransmitter plays a crucial role in the modulation of the cognitive function, working memory and/or attention of the prefrontal cortex and the hippocampus. Dopamine is also a known inhibitory modulator of thyroid stimulating hormone (TSH) secretion. The involvement of dopamine and dopaminergic receptors in neurodevelopment, as well as TSH modulation, led us to hypothesize that excessive manganese exposure may lead to adverse neurodevelopmental outcomes due to the disruption of thyroid homeostasis via the loss of dopaminergic control of TSH regulation of thyroid hormones. This disruption may alter thyroid hormone levels, resulting in some of the deficits associated with gestational exposure to manganese. While the effects of manganese in adult populations are relatively well documented, comprehensive data on its neurodevelopmental effects are sparse. Given the importance of this topic, we review the potential participation of thyroid hormone dyshomeostasis in the neurodevelopmental effects of manganese positing the hypotheses that manganese may directly or indirectly affect thyroid function by injuring the thyroid gland or dysregulating dopaminergic modulation of thyroid hormone synthesis.

## 1. INTRODUCTION

Little is known about the relationship between manganese and thyroid hormone homeostasis in humans. As an enzymatic cofactor, manganese plays an important role in a number of

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physiologic processes; for example, the principal detoxifier of reactive oxygen species in the mitochondria, Mn-SOD, requires manganese for activity. However, when present at high tissue concentrations manganese can exhibit cellular toxicity, particularly in the brain. Exposure to high levels of manganese during fetal development can result in neurocognitive deficits, while in adults; manganese accumulation in the basal ganglia can lead to decreased dopamine levels and cell death in a syndrome called manganism, which shares multiple features with Parkinson's disease.

Dopamine, a major neurotransmitter, is also a regulator of both TSH activity and TSH subunit secretion. Furthermore, dopamine and dopaminergic receptors are involved in neurodevelopment. We therefore hypothesize that abnormal control of thyroid hormone synthesis and function may underlie the neurotoxicity associated with exposure to manganese during fetal neurodevelopment. To date no experimental research has been conducted to elucidate this relationship. Alternatively, manganese may also directly affect thyroid hormone homeostasis, independent of dopamine dysregulation. Support for both hypotheses is discussed, though it needs to be acknowledged that data is sparse, as the subject matter has received little experimental attention.

## 1a. Thyroid Hormone Synthesis and Activation

The thyroid hormones, 3,5,3′-triiodotyronine (T3) and its precursor, namely the "prohormone" thyroxine (T4) are iodinated compounds, synthesized by the thyroid gland, essential for cellular metabolism and for normal central nervous system development (Bernal and Nunez 1995;Chan and Kilby 2000). Thyroid hormones influence gene expression in virtually every vertebrate tissue. Thyroid hormone signaling is mediated by the interaction of nuclear thyroid hormone receptors (TRs) with specific target gene promoters, repressing or enhancing transcription. The binding of thyroid hormone to the TRs can modulate this process, resulting in alterations in the composition of the transcriptional complex. Iodothyronine deiodinases are enzymes that can activate and inactivate thyroid hormones (Bianco and Kim 2006). Deiodinase activity is important in the metabolism, signaling and regulation of thyroid hormones since more than 80% of brain T3 is produced by deiodinase II (D2) conversion of T4 to T3 at the tissue level and not by direct T3 synthesis by the thyroid gland (Crantz et al. 1982,Courtin et al. 1986,Courtin et al. 1988,Leonard 1988). The deiodinases can activate thyroid hormones, mostly within the target cells, by converting T4 to T3 through the removal of an outer ring iodine atom (Bianco and Kim 2006). Deiodinases can inactivate T4 by the removal of an inner-ring iodine atom to the inactive reverse triiodothyronine (rT3) and by sulfation (Esfandiari et al., 1994). It has been speculated that manganese interferes with thyroid hormone binding, transport, and activity at the tissue level (Buthieau and Autissier 1983). In this literature review we examine the potential contribution of thyroid hormone dyshomeostatsis as well as the dopaminergic effects of manganese to the neurodevelopmental effects of manganese.

## 1b. Manganese Deficiency

Manganese deficiency can result in a host of ailments, including impaired growth, poor bone formation and skeletal defects, reduced fertility and birth defects, abnormal glucose tolerance, and altered lipid and carbohydrate metabolism (Freeland-Graves and Llanes 1994;Keen et al., 1999). Suboptimal manganese status may occur in humans with epilepsy, osteoporosis, or exocrine pancreatic insufficiency, individuals undergoing chronic hemodialysis, and in children with Perthes' disease or phenylketonuria (Carl and Gallagher, 1994;Freeland-Graves and Llanes, 1994). Young men placed on a manganese-depleted diet developed an erythematous rash on their torsos (Friedman et al., 1987). Manganese deficiency has also been observed in animals. In a two-generation female rat study, diets extremely low in manganese concentration (0.1 mg Mn/kg) led to impaired growth, increased the activity of hepatic 5′

deiodinase (5′D-I), and an increase in the relative concentrations of T3 in their offspring (Eder et al 1996). However, the concentrations of T4 and free T4 (FT4) remained unchanged.

### 1c. Manganese Toxicity in Humans

In adult humans, manganese toxicity is a well-recognized occupational hazard. Inhalation of particulate manganese compounds (e.g., manganese dioxide [$MnO_2$] or manganese tetroxide [$Mn_3O_4$]) can result in an inflammatory response in the lungs of animals and humans. Respiratory symptoms include cough, bronchitis, pneumonitis, and impaired pulmonary function (Roels et al., 1987). These effects may reflect an indirect response to inhaled particulate matter or may be associated with direct pulmonary toxicity induced by manganese.

Manganese-induced neurotoxicity, also known as manganism, most commonly occurs in workers that have been chronically exposed to aerosols or dusts that contain extremely high levels of manganese (> 1-5 mg/$m^3$) (ATSDR, 2000;Mergler et al., 1994;Pal et al., 1999). Neurotoxicity has also occurred from the consumption of well water containing high levels of manganese (1.8 to 14 mg/L) (Kawamura et al., 1941; Kondakis et al., 1989). Clinical presentations of manganism include diminished motor skills and psychological disturbances, symptoms that parallel those of Parkinson's disease. Elevated brain levels of manganese are observed primarily in those areas which contain high concentrations of nonheme iron, especially the caudate-putamen, globus pallidus, substantia nigra, and subthalamic nuclei. These high levels of manganese, specifically in the substantia nigra have been associated with metal dependent reactive oxygen damage to dopaminergic cells (Oikawa et al 2006). As a result of this cellular damage, manganism is initially characterized by the psychiatric disorder, locura manganica with symptoms including compulsive or violent behavior, emotional instability, and hallucinations. Other early manifestations of manganese neurotoxicity include fatigue, headache, muscle cramps, loss of appetite, apathy, insomnia, and diminished libido. As exposure to manganese continues and the disease progresses, patients may develop prolonged muscle contractions (dystonia), decreased muscle movement (hypokinesia), rigidity, and muscle tremors (Pal et al., 1999). These signs are associated with damage to dopaminergic neurons within brain structures that control muscle movement.

### 1d. Manganese and Fetal Brain Development

The effects of manganese on the adult mammalian brain have received considerable attention. On the other hand, the risk of manganese-induced neurotoxicity during brain development, both pre- and postnatally, has received relatively little attention. Several reports document the neurotoxic effects of manganese on children at various developmental stages following excessive exposures to this metal (Cawte, 1985;Fell et al., 1996;Wasserman et al., 2006;Woolf et al., 2002). Wasserman et al. (2006) suggest that high levels of manganese in drinking water (>300 μg Mn/liter) are associated with reduced intellectual function in children.

More extensive experimentation on the effects of manganese on the developing brain has been conducted in rodents. Neonatal rodents are at an increased risk for manganese-induced neurotoxicity compared to adults due to their ability to achieve higher brain manganese levels and altered brain dopamine concentrations following similar oral exposures (Chandra and Shukla, 1978;Dorman et al., 2000;Kontur and Fechter, 1988;Pappas et al., 1997). Known pharmacokinetic processes that may contribute to the increased susceptibility of neonatal animals to manganese include increased absorption from the gastrointestinal tract, an incompletely formed blood-brain barrier, and the virtual absence of biliary manganese excretory mechanisms until weaning (Ballatori et al., 1987). Manganese concentrations that are necessary during normal fetal rat brain development are higher than in all other age groups, suggesting that manganese is required in a high amount during infancy, and that a sufficient manganese supply is critical for normal brain development (Takeda et al., 1994). This known

high requirement for manganese for optimal neurodevelopment in the neonate (vs. adult) likely reflects the higher net increase in brain manganese concentrations and should not necessarily be construed as evidence for neurotoxicity.

## 2. THYROID HORMONES AND THE BRAIN

Thyroid hormones are essential for normal human brain development and have been implicated in the survival, proliferation, migration, arborization and expression of specific phenotypic markers of neurons (Heisenberg et al., 1992,Muller et al., 1995,Gomes et al., 2001,Konig and Moura Neto, 2002). Thyroid hormones also exert indirect effects, which are mediated by astrocytic secretion of growth factors (Gomes et al., 1999,Martinez and Gomes 2002,Trentin et al., 2003). A deficiency in thyroid hormones during perinatal development leads to irreversible motor and intellectual deficits (Bernal and Nunez 1995;Arnold et al., 2003), with underlying cytoarchitectural changes (Lavado-Autric et al. 2003). The bioavailability of the receptor-active thyroid hormone, T3, is determined by thyroidal synthesis, binding proteins availability, deiodinase metabolism and the rate of catabolism.

Sulfation plays a key role in regulating the biological activity of numerous neurotransmitters, steroid hormone biosynthesis, catecholamine metabolism, and thyroid hormone homeostasis. Sulfation also provides the major mechanism for protection against chemical damage during human fetal development. In adult humans, the vast majority of catecholamines such as dopamine are present in the circulation as their respective sulfate conjugates (the plasma free dopamine (<0.1 pmol/mL) represent less than 1% of the total combined free and sulfate-conjugated dopamine) (Kopin 1985). Sulfate conjugates may be thought of as biologically inactive forms of these biogenic amines, which provide a source of the active, free compounds in target tissues through enzymatic hydrolysis as well as providing an appropriate route of excretion. Sulfation, catalyzed by sulfotransferase enzymes (SULTs), is an important pathway of thyroid hormone metabolism by which T4 is irreversibly converted to the inactive rT3 rather than the active T3 (Visser 1994;Richard et al., 2001), thus sulfation likely plays a key role in regulating the amount of receptor-active thyroid hormone in target tissues. The human fetus and neonate have high levels of circulating sulfated iodothyronines. Both SULT1A1 and SULT1A3, the isoforms of SULT, are expressed at low levels in most fetal brain regions (Richard et al., 2001). The germinal eminence, where the majority of neuroblast cell division occurs in the developing mammalian brain, appears to be the principal site of expression of SULT1A3. Both isoforms of SULT have very broad substrate specificities, including iodothyronines (predominantly T2 and T3) and many xenobiotics. Thus, they may have an important detoxification function during the critical stages of development.

During the second half of gestation, the choroid plexus is also a major site of expression of SULT and of the sodium iodide symporter (NIS), which transports iodide ions from the cerebrospinal fluid, initiating local thyroid hormone metabolism. Selective expression of SULT in the choroid plexus of the fetal brain is intriguing as the choroid plexus (that comprises the blood-cerebrospinal fluid barrier) is the most highly vascularized region of the developing brain. Therefore, it is a potential point of entry for circulating toxins that may result from maternal exposure. It seems reasonable for this tissue to have a high degree of chemical defense and detoxification mechanisms, such as UDP-glucuronosyltransferases and cytochromes P450, which have both been observed in the choroid plexus and in blood-brain interfaces in adult rats (Ghersi-Egea et al. 1994). In fact, the activities of some metabolic enzymes in choroidal tissue are exceedingly high, suggesting that the choroid plexus represents a major site of drug metabolism, functioning to protect the brain from toxic compounds, like manganese. Furthermore, divalent metal transporter (DMT1) exists in neurons, cerebral capillary endothelial cells (that constitute the blood-brain barrier) and choroid plexus (Burdo et al., 2001). The presence of DMT1, a major transporter for manganese is functionally important

with regard to the necessity of stable homeostasis of manganese in extracellular fluids for optimal brain function (Wang et al., 2006). It is also noteworthy that within 5 minutes of systemic administration of manganese in the rat, significant enhancement of manganese by magnetic resonance imaging (MRI) is inherent to the choroid plexus, which spreads to the CSF space in ventricles and periventricular tissue (Aoki et al., 2004).

## 3. MANGANESE, THYROID HORMONE, AND DOPAMINE

### 3a Manganese and Thyroid Hormone

Very little is known about the interrelationships between manganese and thyroid hormones both in development and during adult life. We will focus herein on the former, acknowledging that support for our hypothesis is relatively sparse, given the lack of attention to this issue. We also wish to note, that despite our emphasis on dopamine (see below) that other neurotransmitters may also be subject to dysregulation by manganese. Clearly, more studies are needed.

We posit that manganese may affect thyroid hormone homeostasis and neurodevelopmental processes as a result of both direct dysregulation at the level of the thyroid gland and thyroid hormones, or indirectly via alterations in dopaminergic control of the thyroid gland and its hormones. Dopamine is a known modulator of both TSH and TSH subunit secretion. The damaging effects of manganese to dopaminergic neurons (should they be inherent to prenatal or early postnatal exposure) may result in profound effects on thyroid hormone synthesis at the level of the thyrotroph in the thyroid due to TSH changes. Thyroid hormone, in turn, plays a prominent role in promoting neurodevelopmental process, such as synaptogenesis, synaptic vesicle and receptor recycling, neurotransmitter reuptake, and growth factor receptor signaling (Rami and Rabie, 1990,Heisenberg et al., 1992,Muller et al., 1995,Gomes et al., 2001,Konig and Moura Neto 2002). Accordingly, manganese-induced perturbations in thyroid hormone levels secondary to dopaminergic neuron damage can result in neurodevelopmental deficits.

An additional effect of manganese on thyroid hormones homeostasis may be mediated through their metabolizing enzymes. Current data suggests that manganese can affect thyroid hormones directly by regulating the deiodinase enzymes. An early study of subjects with thyroid disease by Aihara et al. (1984) examined manganese metabolism in hypothyroid, hyperthyroid and euthyroid patients. There were no statistically significant differences in manganese concentrations between patients with thyroid diseases- whether it be overt hyperthyroidism or overt hypothyroidism- and the control subjects. However, a significant correlation was seen between erythrocyte manganese concentrations and circulating T4 ($r=0.230$, $p<0.05$) or T3 ($r=0.275$, $p<0.05$) concentrations, suggesting that thyroid hormone may affect manganese metabolism (Aihara et al., 1984). These results were supported by a study designed to demonstrate hormonal control of Mn uptake by the thyroid. Mice were pretreated for six days with T3 or with propylthiouracil (PTU), a thionamide that decreases thyroid hormone synthesis. The mechanism of action of PTU is inhibition of the synthesis of thyroid hormones by blocking oxidation of iodine in the thyroid gland, thereby blocking the synthesis of T4 and T3 and thus causing an increase in serum TSH. Mice were then injected (i.p.) with radioactive $^{54}$Mn in order to measure manganese thyroid-to-serum concentration ratio (T/S) (Nishida and Kawada, 1992). The T/S of $^{54}$Mn was reduced by preincubation with T3 and enhanced by pretreatment with PTU. Furthermore, there was no change in thyroid gland weights, suggesting that T3 uptake was dependent on changes in the physiological functions of the thyrocytes (not on an increase in thyrocyte numbers). The authors concluded that manganese uptake by the thyroid is controlled by serum TSH and thyroid hormone concentrations. Another study examined the role of manganese in goiter development (Kawada et al., 1985). Mice were fed excessive amounts of manganese while iodine concentrations in the diet remained at normal levels. After seven weeks, the thyroids obtained from treated female mice were enlarged, while those from

male mice did not become goitrous. Serum levels of T4, but not T3 were slightly reduced by manganese, and the thyroid morphology showed retention of colloid in the lumen. The slight reduction in serum T3 could be explained by an increase in T4-to-T3 conversion by deiodinases due to the lower levels of T3.

To examine the effect of manganese on the regulation of thyroid hormone, rats were treated with a manganese-rich diet (10 mg/kg/day as manganese sulfate [$MnSO_4$]) for a period of five weeks (Buthieau and Autissier, 1983). High accumulation of manganese in the pituitary gland resulted in a significant decrease in serum T4, T3, and in TSH concentrations. No change in thyroidal T4 and T3 concentrations were observed. Given that binding of TSH to thyroid plasma membranes is strongly inhibited by neutral salts at relatively low concentrations, manganese probably contributes to a decrease in the binding of TSH to the thyroidal plasma membrane. The decrease in binding would then result in higher circulating TSH levels which, through negative feedback, would inhibit release of TSH from the pituitary gland. It is expected that the decrease in T4 levels would be followed by an enhanced pituitary TSH secretion. In agreement with other studies this study suggests that the role of manganese in thyroid hormone regulation and metabolism is not directly mediated by thyroid hormone synthesis.

### 3b. Manganese-Induced Thyroid Toxicity in Animal Studies

Manganese may also affect thyroid hormone levels by inducing toxicity in the thyroid itself, e.g., effects that are dopamine-independent. Manganese-induced thyroid toxicity was studied in mice and rats fed exceedingly high levels of manganese (3,900 mg/kg/day and 1,300 mg/kg/day for 14 days, <1,950 mg/kg/day for 13 weeks and 2-years of 232 mg/kg/day as $MnSO_4$). These studies (National Toxicology Program 1993) revealed no effects of manganese on the formation of pathological lesions in the thyroid. However, in a 2-year mouse study, thyroid follicular hyperplasia and dilatation were observed in males fed 584 mg/kg/day, and thyroid follicular hyperplasia was observed in females fed 64 mg/kg/day (National Toxicology Program, 1993).

## CONCLUSIONS

Many questions still remain concerning the relationship between manganese and thyroid hormones. Although not conclusive, experimental findings point to the ability of manganese to interfere with deiodinase activity thus affecting circulating thyroid hormone concentrations. The role of manganese uptake by the thyroid gland is still unclear and the potential mechanisms by which it may directly affect thyroid hormone homeostasis or function remain to be elucidated; however, dose-dependent goitrogenic effects of manganese have been illustrated. It is also noteworthy, that effects of manganese on optimal brain dopamine concentrations, which in turn, affect thyroid hormone homeostasis, may alter the regulatory function of thyroid hormone, both in developing and mature animals. Similarly, manganese may affect a plethora of other neurotransmitters, in turn, causing dysregulation of thyroid hormone homeostasis. While the effects of manganese on the mature nervous system are relatively well understood, its effects on neurodevelopment have received little experimental attention. The hypotheses posited in this review are testable and clearly warrant future experimental exploration.

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