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Cardiovascular Toxicities Upon Manganese Exposure

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Abstract

Manganese (Mn)-induced Parkinsonism has been well documented; however, little attention has been devoted to Mn-induced cardiovascular dysfunction. This review summarizes literature data from both animal and human studies on Mn's effect on cardiovascular function. Clinical and epidemiological evidence suggests that the incidence of abnormal electrocardiogram (ECG) is significantly higher in Mn-exposed workers than that in the control subjects. The main types of abnormal ECG include sinus tachycardia, sinus bradycardia, sinus arrhythmia, sinister megacardia, and ST-T changes. The accelerated heartbeat and shortened P-R interval appear to be more prominent in female exposed workers than in their male counterparts. Mn-exposed workers display a mean diastolic blood pressure that is significantly lower than that of the control subjects, especially in the young and female exposed workers. Animal studies indicate that Mn is capable of quickly accumulating in heart tissue, resulting in acute or sub-acute cardiovascular disorders, such as acute cardiodepression and hypotension. These toxic outcomes appear to be associated with Mn-induced mitochondrial damage and interaction with the calcium channel in the cardiovascular system.

Key Words: Manganese; occupational exposure; cardiovascular toxicity; ECG; hypotension; vasodilatation.

Introduction

Manganese (Mn) is an essential trace element, overexposure to which can cause toxicities. The major source of environmental contamination has been related to mining and processing of Mn and/or steel manufacture *(1)*. Other sources of exposure include the production of Mn alloys such as with bronze, nickel, and copper, manufacture of dry-cell batteries, use of Mn salts in chemical industries, and addition of organic Mn compounds, such as methylcyclopentadienyl Mn tricarbonyl (MMT); Mn is also an antiknock agent in gasoline and is released in the welding practice *(2–6)*.

The clinical manifestations of Mn intoxication are characterized by extrapyramidal dysfunction and neuropsychiatric symptoms *(6,7)*. Whereas Mn neurotoxicities are well recognized and documented, the effect of Mn on the cardiovascular system has received less attention. In fact, some researchers have pointed out that the Mn toxicity to cardiac muscle cells as well as cardiac tissues that has been observed in

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in vitro or *in situ* studies may not necessarily happen in vivo to animals or humans *(8)*. However, the observation made by Kobert, dated as early as 1883 *(9)*, suggests that Mn salts can induce a fall in the blood pressure; this is subsequently substantiated by a series of early experiments performed on animal models including rat, cat, and dog *(10–13)*. Nonetheless, to the best of our knowledge, there has been no comprehensive review in literature to assess Mn's toxicity to the cardiovascular system, particularly in human intoxication cases. This article evaluates the current understanding of Mn exposure and cardiovascular function. The results from animal studies will be first discussed, followed by the literature survey of Mn cardiovascular toxicities in humans.

Mn Cardiovascular Toxicities Observed in Animal Studies

Effect of Mn Exposure on Myocardial Contraction

Chronic exposure to Mn has been associated with a decline in myocardial contraction *(13–17)*. Following intravenous injection of 0.5–5 mg Mn/kg as $MnCl_2$, the P-R and Q-T intervals were prolonged and the QRS wave was broadened *(17)*. The weakened myocardial contraction appeared to be due to Mn's direct effect on mitochondrial function. For example, when rats were fed with 1000 mg Mn/kg by oral dose for 8 wk, the mitochondrial swelling along with vacuoles in cardiac myocytes were evident as seen by electron microscopy *(14)*. The same study also showed a decrease in cytochrome oxidase and succinate dehydrogenase activity in myocyte mitochondria. These authors suggest that Mn exposure may damage the myocyte cytoplasmic membrane, increase mitochondrial membrane permeability, and cause mitochondrial vacuolation. The altered mitochondrial function thus contributes to a decline in cardiac contraction.

In a separate study in which rats were intraperitoneally injected with $MnCl_2$ at 40 mg/kg daily for 5 wk, although the blood concentration of Mn was increased, the selenium level was significantly decreased, and so was the activity of glutathione peroxidase in blood samples. Moreover, there was a polarized mitochondrial fluorescence in myocytes along with significantly increased viscosity, suggesting that Mn may reduce the membrane fluidity of mitochondria in rat myocyte *(16)*.

The in vitro results support Mn toxicity on cardiac function. When the isolated rat heart was perfused with 10 or 100 μmol/L $MnCl_2$ for 10 min, the Mn concentration in heart tissues was significantly increased in concert with a great reduction in contraction, whereas Mg and Ca contents were decreased *(18)*. The cardiac contraction became evidently weakened after perfusion with Mn for 5 min at the high dose. The rate of myocardial contraction turned to negative when Mn concentration was maintained at or above 300 μmol/L in the perfusion fluid. The same group of researchers also indicated that Mn toxicity on cardiac contraction was reversible, because the contraction could resume rapidly after Mn was removed (or washed) from the tissue preparation *(19,20)*.

At the high concentration of exposure (1–8 mmol/L), Mn not only inhibits myocardial contraction, but also shortens the action potential durability, affects the refractory period (ERP), and decreases the maximum rising velocity (V_{max}) of zero value action potential *(21)*. The in vitro study also demonstrates that Mn at 0.5 mmol/L markedly induces the repressed electrophysiological activity of atrionector with a decline in action potential amplitude (APA), weakened V_{max}, altered 4 phase slope (SP_4), and slowed sinus pulsation. The authors suggest that all this may be due to the blocked slow channel and inhibited Ca^{2+} influx by Mn *(21)*. These and other experimental data on Mn cardiotoxicity are summarized in Table 1 *(13–25)*.

Mn is present in the air mainly in the form of oxidized particles. To study the association between airborne Mn particles and changes in cardiovascular morbidity and mortality, Muggenburg et al. *(26)* exposed conscious beagle dogs to aerosol Mn at concentrations of 0.05 mg/m^3 by inhalation for 3 h daily for three successive days. The ECG was then recorded and evaluated for exposure-related changes in heart rate, heart rate variability, and abnormalities of waveforms. The authors reported a potential association between age and cardiovascular susceptibility factors underlying the clinical abnormalities; however, there was no significant relationship between the abnormal ECG of these dogs and Mn exposure. Thus, the authors concluded that short-term exposure to respirable oxide and sulfate forms of Mn particles had little effect on the ECG of dogs having preexisting cardiac abnormalities.

Table 1
Evidence of Mn Toxicity on Cardiac Function From Animal Studies

Species	Dose	Toxicity observed	Ref.
Rat	>25 μ*M*	Negative inotropic effect	*13,22*
(isolated heart)	300 μ*M*	Negative chronotropic effect	*22,23*
	160 μ*M*	Negative chronotropic effect	*23,24*
	3000 μ*M*	Ventricular fibrillation	*22,23*
	10–100 μ*M*	Depression of contractile function	*18*
	=30 μ*M*	Depression of contractile function	*19*
	=300 μ*M*	Negative chronotropy	*19*
	1000 μ*M*	Depressed cardiac function	*20*
Rat	1000 ppm, p.o.	Swelling, injured cristae and vacuolation	*14,15*
(cardiac myocyte mitochondrion)		Decreased cytochrome oxidase and succinate dehydrogenase Increased membrane permeability	
	40 ppm, ip	Decreased membrane mobility	*16*
Guinea pig	4 m*M*	Depression of contractile function	*21*
(cardiac myocyte)	0.2–0.4 m*M*	Inhibited spontaneous electrophysiological activity	
Dog	5 ppm	Decreased heart rate	*17*
	1–5 ppm, IV	Prolonged P-R and Q-T interval, widened QRS wave	*17*
Conscious dog	>30 μ*M*, IV	Increased heart rate	*24*
Dog, rabbit	10–100 μ*M*, IV	Prolonged P-R and Q-T intervals Tachycardia Slowed heart rate	*25*

Mn Exposure and Cardiac Ca Status

One of the possible mechanisms of Mn-induced cardiac toxicity may pertain to altered Ca dynamics in cardiac myocytes. Dudek and Pytkowski *(27)* exposed rats in vivo to Mn^{2+} at 0.25 mmol/kg by daily oral gavage for 14 d and studied the effects of Mn on Ca^{2+} exchange and the contractile force of ventricular myocardium. By using ^{45}Ca, the authors were able to calculate cellular Ca^{2+} content by subtracting Ca^{2+} in the extracellular space from the total tissue Ca^{2+} content. Fourteen days following Mn exposure, the exchangeable Ca in the Mn-treated group was increased by 52% as compared with controls. By recording the left-ventricular pressure (dP/dt) via a balloon catheter inserted into the left ventricle, the authors also observed that the maximal ventricular developed pressure (P_{max}) and the maximal left-ventricular pressure (dP/dt_{max}) were increased by 35% and 228%, respectively, in comparison with control rats, following 14 d of Mn administration *(27)*.

Recently, Tanake and his colleagues *(28)* reported that in a guinea pig ventricle experimental model, Mn caused the initial depression but late augmentation of contractile force. Mn exposure shortened the action potential duration under normal conditions, but it prolonged the duration under Ca^{2+}-free conditions. When applied to fura-2-loaded ventricular myocytes, Mn markedly quenched the cytoplasmic fluorescence excited at a 360-nm wavelength. Thus, it appeared that Mn caused the decreased contractile force by blocking the L-type Ca^{2+} channel. Moreover, Mn may enter the cytoplasm through the Ca channel and produce the late augmentation of the contractile force by enhancing sarcoplasmic reticulum function *(28)*.

Mn Toxicity on Blood Vessels

Mn is a known vasodilator; the hypotension following acute exposure to the high dose of Mn has been documented *(9,17,29–30)*. When dogs were perfused with 10 mg Mn/kg as $MnCl_2$ daily for 4 d via the inferior vena cava, there was a significant decrease in blood pressure accompanied by a reflex tachycardia *(29)*. In an acute exposure experiment, six dogs were intravenously injected with Mn at 10 mg/kg. Profound hypotension and severe bradycardia developed, followed by eventual death *(24)*. Another study on the dog with intravenous perfusion of Mn (15–25

μmol/L) for 20 min also shows a dose-related coronary vessels relaxation *(30)*.

Effect of Mn on α-Adrenergic Receptor in Blood Vessels

The exact mechanism by which Mn dilates blood vessel remains uncertain. However, several studies have suggested that Mn may act on the α-adrenergic receptor (AR). Phenylephrine is an α-1 AR agonist that induces vasoconstriction. In isolated rat thoracic aorta rings, low doses of Mn exposure (0.3, 1, 3 μ*M*) inhibit phenylephrine-mediated contraction in a dose-dependent manner. The authors suggest that variations in plasma concentrations of Mn can lead to an altered α-1 AR-mediated constrictive response *(31)*.

The results from recent in vivo dietary Mn exposure experiments also support Mn action on α-1 AR *(32)*. Weanling rats were fed with an Mn-deficient diet (MnD, <1 ppm Mn), an Mn-adequate diet (MnA, 10–15 ppm Mn), or an Mn-supplemented diet (MnS, 45–50 ppm Mn). After 15 wk on the diets, the thoracic aortas were isolated and treated with the α-1 AR agonist L-phenylephrine (10^{-8} to 3×10^{-6} *M*) to assess the maximal force (F_{max}) of contraction and relaxation, as well as the vessel sensitivity (pD). MnS-fed animals showed a low F_{max} when the blood vessel preparation was stimulated with L-phenylephrine, suggesting that dietary Mn at levels of 45–50 ppm affected the contractile machinery by reducing maximal vessel contraction in response to an α-1 AR agonist. In contrast, the pD values were significantly greater in the MnD group than in MnA and MnS animals, respectively, again indicating that a restriction of dietary Mn could affect vascular sensitivity to the α-1 AR agonist. One of the important implications of this study is that these results establish a clear relationship between dietary Mn exposure and vascular smooth muscle's ability to respond to an α-1 AR agonist *(32)*.

Effect of Mn on Arginase- or Ca-Mediated Vasoconstriction

Arginase plays a critical role in the breakdown and removal of nitrogen from the body, a process known as the urea cycle. The lack of the arginase enzyme or a weakened arginase activity results in the excessive accumulation of nitrogen as ammonia in the blood, as well as arginine in the blood and cerebrospinal fluid. Arginase activity is also sensitive to Mn tissue concentration *(33)*. A recent study by Ensunsa et al. *(34)* demonstrates that dietary Mn deficiency in rats reduces arginase activity and enhances endothelium-dependent vasorelaxation in rat aorta. However, whether or not overexposure to Mn affects arginase activity and results in the opposite effect remains unknown.

Mn dipyridoxyl diphosphate (MnDPDP) is a widely used diagnostic contrast agent. The Mn released from MnDPDP during diagnostic imaging may have a direct effect on vasoconstriction. Studies based on isolated perfused rat hearts, isolated bovine mesenteric arteries, or dogs with acute ischemic heart failure have demonstrated that Mn at high concentrations acts as a calcium antagonist to cause negative inotropy, whereas at low concentrations it acts as an effective superoxide scavenger, conserving nitric oxide and facilitating vasodilatation. Thus, to acute ischemic heart failure, application of MnDPDP appears to be beneficial rather than detrimental. Some authors observe that Mn could maintain or elevate heart rate and blood pressure, and does not worsen the existing cardiac failure. MnDPDP appears to be about 10 times less potent than $MnCl_2$ in eliciting these cardiovascular responses *(35,36)*. Table 2 summarizes general experimental observations on Mn vascular effect *(17,19,22–25,30)*.

Mn Cardiovascular Toxicities in Mn-Exposed Workers

Cardiac Effects of Mn Occupational Exposure

From the occupational exposure point of view, our own studies suggest that chronic Mn exposure can cause significant cardiovascular toxicities. In a study from a smelting manufacturer producing Mn, the geometric mean concentration of airborne Mn (as MnO_2) in the working environment was 0.07 mg/m^3. We found that the heart rates were significantly faster and the P-R intervals were significantly shorter in female smelting workers than those of female controls. QRS waves and T waves were also wider and more elevated, respectively, in both male and female smelting workers than in controls. These data suggest that the low level of Mn exposure among smelting workers appears to have a significant effect on their cardiac function *(37,38)*.

Table 2
Evidence of Manganese Toxicity on Vascular Functions From Animal Studies

Species	Dose	Effect	Ref.
Rat (isolated heart)	15, 25 μ*M*	Dose-dependent line broadening and coronary vasodilatation	*30*
	>25 μ*M*	Rise in aortic pressure	*22,23*
	30–1000 μ*M*	Raised coronary vascular resistance	*19*
	3000 μ*M*	Overcome the vasoconstrictory response	
Bovine (isolated arteries)	1 μ*M*	Endothelium-dependent relation	*24*
Dog	10 ppm, IV	Lethal following brief, profound hypotension and bradycardia	*17*
	16 ppm, IV	Hypotension with reflex tachycardia	*30*
	>30 μ*M*, IV	Increased blood pressure	*24*
Dog, rabbit	10–100 μ*M* IV	Dose-dependent drop in arterial pressure (at 1 min), reverted at 15 min	*25*

When the geometric mean concentrations of airborne MnO_2 in the working air were between 0.05 and 2.15 mg/m^3, the incidences of abnormal ECG in workers were markedly increased as compared with the control subjects. The main types of abnormal ECG were sinus arrhythmia and ST-T changes. These incidences were positively correlated with the concentration of airborne MnO_2 in the working environment, and had the tendency to increase with the increased working years among exposed workers. The diagnostic correct rate of the abnormal ECG was correlated well with the abnormal blood pressure *(39)*. Our finding has been confirmed by other investigators. When the geometric mean concentration of MnO_2 in the working air was between 0.14 and 0.20 mg/m^3, the incidence of abnormal ECG in exposed workers was significantly higher than that of control workers *(40,41)*.

Mn's effect on cardiac function appears to be job category-related as well. In another study of our own on the workers who were exposed to Mn dust, the airborne Mn concentration was 0.13 mg/m^3 in the working area. The enumeration data, however, did not show any relationship between ECG changes and the level of Mn exposure, although some Mn-exposed workers did experience the vascular disorders *(42)*. Even at the geometric mean concentration of 1.96 mg/m^3 in the milling working environment, the main complaints were headache, dizziness, sleeping disorder, fatigue and memory loss, yet the abnormal OR was not observed in exposure workers, neither was the ECG among exposed workers abnormal in comparison with control subjects *(43)*.

Among ferroalloy workers, the toxic effects due to Mn exposure appear to be associated with drowsiness, inertia, memory loss, enhanced myotatic reflex, hand and tone tremor, abnormal finger-to-nose position, and observable Romberg's sign. However, ECG does not seem to be significantly abnormal in exposed as compared with control groups *(44)*. Studies conducted among workers exposed to iron-Mn and silicon-Mn in 12 ferrite factories also suggest that, although the accidental mortality was increased, the total death due to cardiovascular disorders was not changed among Mn-exposed workers as compared with control subjects. However, the mortality from three hypertension-related diseases combined (cerebrovascular, hypertensive, and renal diseases) showed an identical arising mortality trend as the function of work year among the ferrosilicon/silicon-metal workers as well as in iron-manganese/silicon-manganese furnace workers *(45)*. Another study on furnace dust exposure suggests that pneumonia induced by Mn could reduce the pulmonary function of workers, which may be associated with ischemic cardiac diseases *(46)*.

Vascular Effect of Mn Occupational Exposure

Similarly to findings from animal studies, Mn exposure has an apparent effect on the vascular system. For example, the clinical application of a magnetic resonance imaging (MRI)-enhancer MnDPDP reportedly produces flushed face and hot feeling on the head and ear. Postural hypotension has also been observed in MnDPDP-overdosed patients *(47)*.

As mentioned previously *(42)*, the milling workers who were exposed to Mn dust did not show a significantly altered cardiac function. However, the

mean diastolic pressure of these workers was significantly lower than that of control subjects, and the incidence of diastolic hypotension in these Mn-exposed workers was significantly higher than that in controls. The diastolic pressure among Mn-exposed workers tended to decline with the increase of exposed time and age. We also found that the incidence of diastolic hypotension was significantly higher in the age group of 20–30 yr than in other age groups, and significantly higher in female workers exposed to Mn than in their male counterparts. It appears that young and female workers are more susceptible to Mn-induced vascular dilation effect *(42)*. Studies by the other group of investigators also support the view that Mn exposure causes vasodilatation, leading to a decline in diastolic pressure *(44)*. Our recent study further demonstrated that when the workers were exposed to smoke and dust containing high levels of Mn (0.45 mg/m^3), their QRS waves were significantly widened, their T waves elevated, and their mean diastolic blood pressure significantly reduced in comparison with control subjects *(48)*. Saric and Hrustic *(49)* reported the similar finding that the workers with the highest level of exposure to Mn had the lowest systolic blood pressure.

Effect of Mn Occupational Exposure on Autonomic Nervous System

Cardiovascular function is closely regulated by the autonomic nervous system. Thus, it is highly possible that any toxic effect of Mn on the cardiovascular system could be indirectly derived from Mn's effect on the autonomic nervous system. In one case report involving Mn alloy workers, the high-frequency part of a 24-h ECG was significantly decreased among Mn-poisoned workers, suggesting an imbalance in autonomic function. The disorder of autonomic function and the change of heart rate became evident among Mn-exposed workers. Patient emotion related to short-term memory and attention was also changed in four Mn-poisoned workers. Further analysis of 24-h, nonrecumbent ECG showed a reduced reaction of the heart rate in response to parasympathetic nerve activity. Thus, Mn intoxication appears to reduce central parasympathetic nerve function *(50)*.

Another investigation among welders whose blood Mn concentrations (0.09 ± 0.06 μmol/L) were significantly higher than those of control subjects (0.03 ± 0.02 μmol/L) showed that the welders' HR-V, HR-DB, and $R_{max:min}$ were greatly decreased as compared with control subjects. Multiple regression analyses indicated that factors such as age, Mn exposure duration, alcohol drinking, and level of education were all associated with altered heart rate and blood pressure. Based on the clinical data, these researchers conclude that Mn exposure interferes with parasympathetic nerve function; the cardiovascular autonomic nervous system may serve as a target for Mn toxicity *(51)*. Other evidence that supports Mn toxicity on the autonomic nerve system comes from a study conducted in 39 male boilermaker construction workers *(52)*. It should be noted that some airborne particulates, with or without the presence of Mn, may have a nonspecific effect on the autonomic nervous system. Thus, caution must be taken in interpreting particulate data. Table 3 summarizes Mn cardiovascular toxicities observed from human studies *(37–44,48–51)*.

Possible Mechanisms of Mn-Induced Cardiovascular Toxicities

Altered Autonomic Nervous Function

Because the cardiovascular functions are precisely regulated by the autonomic nervous system, a minor alteration in the autonomic function could lead to profound detrimental outcomes in both cardiac and vascular performance. As discussed previously, Mn-exposed workers show a disturbed autonomic nervous function *(50,51,53)*. This disturbance could lead to the change of cardiac rhythm and blood pressure seen in clinics. More detailed studies must be done in order to verify Mn's effect on autonomic nervous function.

Reduced DA, 5-HT, Disturbed Cholinesterase Synthesis, and Reduced Superoxide Dismutase Activity

Dopamine (DA) and serotonin (5-HT) are important neurotransmitters involved in the regulation of cardiovascular functions. Dopamine, by acting on the D1 receptor, causes vasodilatation, whereas 5-HT causes vasoconstriction via binding to 5-HT2 receptors on blood vessels. It is reported that Mn^{2+} reduced cellular dopamine levels more than Mn^{3+}, especially at the highest exposures (50% reduced at 200 μ*M* Mn^{2+}) in PC12 cells. In contrast, Mn^{3+} produced a >70% reduction in cellular 5-HT at all exposure

Table 3
Evidence of Manganese (Mn) Cardiovascular Toxicities From Human Studies

Reference (cases vs controls)	Type of plants	Airborne Mn (mg/m^3)	Cardiovascular effects
Saric et al. *(48)* (367 vs 392)	Ferroalloy	0.39–20.44	Decreased systolic pressure
Jiang et al. *(42)* (547/109 vs 128/26)[a]	Ferroalloy	0.13 (0.10–0.97)	Decreased diastolic pressure
Su et al. *(44)* (45 vs 60)	Mn ferroalloy		Decreased diastolic pressure
Barrington et al. *(50)* (8 cases)	Mn alloy	0.2–1.0	Orthostatic hypotension in a manganism patient
Xie et al. *(39)* (914/446 vs 248/115)[a]	Smelting Mn ore milling	0.05-2.15	Abnormal ECG, hypertension and hypotension
Jiang et al. *(38)* (0/25 vs 0/23)[a]	Ferroalloy	0.07 (0.02–0.29)	Change in heartbeat
Jiang et al. *(43)* (37/18 vs 32/24)[a]	Mn ore milling	1.96 (0.17–22.24)	Negative
Jiang et al. *(37)* (18/18 vs 18/18)[a]	Ferroalloy	0.07 (0.02–0.29)	Change in heartbeat and ECG
Jiang et al. *(49)* (50 vs 50)	Ferroalloy	0.45 (0.15–1.99)	Change in ECG and decreased diastolic pressure
He et al. *(51)* (56 vs 34)	Welding	0.31 (0.08–5.78)	Alteration of cardiovascular autonomic nervous system
Zhang et al. *(40)* (186 vs 182)	Welding	0.20	Abnormal ECG
Ji et al. *(41)* (93/165 vs 109/223)	Ceramics	0.14	Abnormal ECG

[a]Male/female. ECG, electrocardiogram.

levels as compared with Mn^{2+} *(54)*. The differential effects of Mn^{2+} vs Mn^{3+} exposures on cellular toxicity cannot be attributed simply to the different cellular levels of Mn. Thus, the oxidation state of Mn exposures may play an important role in mediating Mn cytotoxicity.

Mn has also been found to disturb the synthesis of cholinesterase, which causes accumulation of acetylcholine (ACh). The disturbed autonomic nervous function can lead to the altered rhythm of the heart as well as of the blood pressure *(55)*.

The superoxide dismutase (SOD), which requires Mn for its activity, plays a significant role in vascular contractility. A diminished SOD activity and an increased superoxide anion level have been linked to oxidative stress-induced vasodilatation *(56)*. However, the study conducted in a rat model has shown that Mn exposure did not cause any significant change in SOD activity in the heart as compared with controls *(57)*.

Blockage of the Ca^{2+} Channel

Mn appears to affect cardiac function by blocking Ca channels; however, a high concentration of Mn is required for such an action. In the heart, Mn appears to block the Ca channel so that the excitation phase is separated from the contraction phase in the myocardium, which ultimately leads to a decrease in the contractibility of the heart. Mn has been found to prolong the conduction time, decrease the action potential amplitude (APA), and decrease the V_{max} and SP_4 in atrioventricular node cells *(21)*. In a rat model, Mn blocks the Ca slow channel and hinders Ca inward flow. The lateral surfaces of ventricular trabecula appear to be the primary target for Mn action. The Ca slow channel possesses a binding site for substrate

Ca. Mn appears to have a higher affinity than Ca for the acceptor-combine site in the Ca slow channel, which explains the inhibitory effect of Mn on the Ca channel *(47)*.

In blood vessels, Mn may also exert similar inhibitor action by blocking the coupling process between excitation and contraction of the vascular smooth muscle. This could contribute to Mn-induced hypotension *(21,47,58)*.

Damage to Myocardial Mitochondria

Within the cell compartment, the mitochondrion is the primary subcellular organelle to accumulate Mn *(59)*. Once inside the mitochondria, Mn can interact with enzymes that are involved in the respiratory chain. Alteration in mitochondrial energy production can compromise the cardiac function. In the test tube, Mn has been shown to inhibit the activity of mitochondrial aconitase, whose function is critical to electron transfer during the production of ATP. The inhibitory effect was reversible and Mn-concentration dependent, and was reversed by the addition of Fe to the reaction mixture *(60)*. In an in vivo chronic Mn exposure model in which rats received an intraperitoneal injection of 6 mg/kg Mn as $MnCl_2$ once daily for 30 consecutive days, Mn exposure led to brain region-specific alteration in total aconitase (i.e., mitochondrial + cytoplasmic) *(60)*. Whether Mn also inhibits myocardial aconitase remains unclear; however, some studies have suggested that excessive Mn may cause a decrease in cytochrome oxidase and succinate dehydrogenase activity in the mitochondrial respiratory chain, a disturbance in oxidative phosphorylation, and a decline in oxygen utilization rate *(15)*, all of which may induce structural and functional alterations of other subcellular organelles and components.

The altered mitochondrial function with Mn exposure could also be due to Mn's toxicity to mitochondrial membrane fluidity. Some evidence has shown that Mn can accelerate the excretion of internal selenium and reduce the activity of GSH-Px . As a consequence, the oxidative stress may cause abnormalities in the components of membrane lipid, and thus the decline of membrane fluidity *(15,16)*. A recent study also shows that Mn is capable of restraining the function of the proton pump and reducing mitochondrial membrane potential, resulting in injury to myocardial cells *(61)*. Apparently, upon accumulating in the mitochondrial matrix, Mn may disrupt mitochondrial function by inhibiting energy transduction, inducing mitochondrial DNA mutation, and enhancing the production of free radicals *(59,62–65)*.

Conclusion

Taken together, both animal and human evidence, although it remains inadequate, supports the view that Mn exposure significantly alters cardiovascular function despite the lack of epidemiological data on cardiovascular morbidity and mortality on Mn workers in the current literature. Mn exposure produces abnormal ECG and inhibits myocardial contraction. With regard to vascular function, Mn exposure dilates the blood vessel and induces hypotension. Mn-induced cardiovascular toxicities appear to be associated with acute or sub-acute exposure in animals and with chronic exposure in humans. However, a well defined clinical characterization of such an Mn cardiovascular toxicity is till lacking. Many critical questions regarding Mn's effect on the cardiovascular system remain unsolved. For example, what is the clinically relevant value to indicate Mn-induced decreases in diastolic blood pressure? Is there any association between Mn-induced cardiovascular toxicities and the workers' working ability? Is there any dose–response relationship between an inner dose of Mn and cardiovascular effect? What are the biological markers that can be used to better define Mn-induced cardiovascular toxicities? Effort in searching for these answers will not only help in preventing Mn toxicity, but also create a new avenue of research in Mn occupational toxicology.

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