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Welders are at risk of being exposed to high concentrations of welding fumes and developing pneumoconiosis or other welding-fume exposure-related diseases. Among such diseases, manganese resulting from welding-fume exposure remains a controversial issue, as although the movement of manganese into specific brain regions has been established, the similar movement of manganese presented with other metals, such as welding fumes, has not been clearly demonstrated as being similar to that of manganese alone. Meanwhile, the competition between Mn and iron for iron transporters, such as transferrin and DMT-1, to the brain has also been implicated in the welding-fume exposure. Thus, the increased signal intensities in the basal ganglia, including the globus pallidus and subcortical frontal white matter, based on T1-weighted magnetic resonance imaging in welders, require further examination as regards the correspondence with an increased manganese concentration. Accordingly, to investigate the movement of manganese after welding-fume exposure, 6 cynomolgus monkeys were acclimated for 1 mo and assigned to 3 dose groups: unexposed, low dose of (total suspended particulate [TSP] 31 mg/m³, 0.9 mg/m³ of Mn), and high dose of total suspended particulate (62 mg/m³ TSP, 1.95 mg/m³ of Mn). The primates were exposed to manual metal-arc stainless steel (MMA-SS) welding fumes for 2 h/day in an inhalation chamber system equipped with an automatic fume generator for 6 mo. Magnetic resonance imaging (MRI) studies of the basal ganglia were conducted before the initiation of exposure and thereafter every month. During the exposure, the blood chemistry was monitored every 2 wk and the concentrations of metal components in the blood were measured every 2 wk and compared with ambient manganese concentrations. The manganese concentrations in the blood did not show any significant increase until after 2 mo of exposure, and then reached a plateau after 90 days of exposure, showing that an exposure period of at least 60 days was required to build up the blood Mn concentration. Furthermore, as the blood Mn concentration continued to build, a continued decrease in the MRI T1 relaxation time in the basal ganglia was also detected. These data suggested that prolonged inhalation of welding fumes induces a high MRI T1 signal intensity with an elevation of the blood manganese level. The presence of a certain amount of iron or other metals, such as Cr and Ni, in the inhaled welding fumes via inhalation was not found to have a significant effect on the uptake of Mn into the brain or the induction of a high MRI T1 signal intensity.

Several pharmacokinetic studies on inhalation exposure to manganese have already demonstrated that manganese readily accumulates in the olfactory regions and brain regions. For example, manganese phosphate-exposed rats showed elevated manganese concentrations in the olfactory bulb, striatum, and lungs following 14 or 90 days of inhalation exposure (Vitarella et al., 2000; Normandin et al., 2002), while 10 to 1000 µg manganese chloride administered intranasally for 1–3 wk to male Sprague-Dawley rats was found to enter the central nervous system (CNS) via the olfactory system and produced an initial effect on the astrocytes (Henriksson & Tjälve, 2000). In addition, a manganese chloride inhalation study using cynomolgus monkeys indicated that manganese shows a selective affinity to the globus pallidus and pituitary (Newland et al., 1989). The kinetics of manganese distribution in primates indicate that inhalation could prolong the exposure of other tissues due to the slow release of manganese (Newland et al., 1987, 1989). The elimination of manganese from the brain after inhalation is about four times slower than after subcutaneous administration, suggesting that manganese deposited in the lungs continues to be supplied to the brain long after exposure has been terminated (Newland et al., 1987, 1989).

However, the absorption and transportation of the manganese from the welding fumes may behave this was due to the influence of various other metals contained in the welding fumes, mainly Fe, Cr, and Ni. Furthermore, the idea of transporters competing for binding sites makes the uptake of Mn to sites in the brain target sites more complicated. A previous study by the current authors on the distribution of Mn in the brains of Sprague-Dawley rats after 60 days of stainless steel welding-fume exposure indicated that the manganese distribution in the brain regions after welding-fume inhalation exposure was different from that of other exposure regimens using Mn-only exposure via inhalation. For example, 90 days of manganese phosphate inhalation exposure produces increased manganese concentrations in all brain tissue, and the increase is dose dependent in the olfactory bulb and caudate/putamen (Normandin et al., 2002). Fourteen days of manganese sulfate and manganese tetroxide inhalation exposure increases the manganese concentrations in the striatum and olfactory bulb (Vitarella et al., 2000; Dorman et al., 2001). Plus, 13 wk of manganese dust inhalation exposure increases the manganese concentrations in the brain regions, including the globus pallidus, frontal cortex, putamen, and cerebellum (St-Pierre et al., 2001). Meanwhile, in primate studies, inhalation exposure to a manganese chloride aerosol for 5 mo results in manganese accumulation in the globus pallidus and pituitary gland, with little effect on the gray and white matter (Newland et al., 1989). All the inhalation studies on rats just described found increased concentrations of manganese in the striatum and globus pallidus, whereas the previous welding-fume inhalation study identified a significant increase in the cerebellum rather than the basal ganglia or striatum, indicating different pharmacokinetics from the manganese-only exposure studies (Yu et al., 2003a). This difference may have been due to a species difference, the dosimetry, and exposure duration. Thus, the different pharmacokinetics of the metal components in welding fumes need to be investigated further using species closely related to humans.

Accordingly, to clarify the manganese distribution in the brain and blood concentration of manganese after welding-fume exposure, nonhuman primate cynomolgus monkeys were exposed to stainless steel welding fumes, their blood concentrations of manganese were monitored, and the manganese distribution on the basal ganglia was examined using magnetic resonance imaging (MRI) technology.
MATERIALS AND METHODS

Generation of Manual Metal-Arc Stainless Steel (MMA-SS) Welding Fumes

The welding fumes were generated using an automatic robotic arm as a holding support for the welding rod (KST 308, 2.6 × 300 mm, Korea Welding Electrode Co. Ltd, Seoul). When the robotic arm approached the base stainless-steel plate (SUS 304, 2.5 cm thick) in a zigzag motion, an arc was produced and the rod was consumed, generating welding fumes. The fumes were then moved into exposure chambers (whole-body type, each 1.5 m³, Dusturbo, Seoul) that were rectangular in shape and made of metal with a Plexiglas window (Figure 1). Each chamber was able to accommodate two monkey cages and the total volume occupied by the 2 monkeys in a chamber was estimated as 1.3%. The chambers were equipped with HEPA filters to provide purified air to the exposure chambers.

The welding fumes in the chamber were sampled using a personal sampler (MSA 484107, Pittsburgh, PA) at a flow rate of 2 L/min. The metal composition of the welding fume particulate captured on membrane filters (pore size 0.8 μm, 37 mm diameter, Millipore AAWP 03700, Bedford MA) was analyzed for metal composition with an inductively coupled plasma analyzer (Thermojeralash, IRIS, Houston, TX) using NIOSH method 7300 (1999). O₃, NO₂, and nitrous fumes were all measured using Dräger tubes (Catalogue numbers 6733181, CH 31001, and CH 30001, respectively) and sampled by stroking a gas detector pump (6400000, Dräger, Lübeck, Germany), according to the manufacturer’s directions, 1 h after the welding-fume exposure began. An Anderson sampler (AN-200, Shibata, Tokyo) was used to measure the mass median aerodynamic diameters of the welding fumes. The flow rate was 28.3 L/min and the sampling time 5 min.

Inhalation Exposure

Six male, 3.7 ± 0.7-kg cynomolgus monkeys (Macaca fascicularis), 63 ± 5 mo old, were purchased from the Yunnan National Laboratory Primate Center (China) and acclimated for a 3-mo period. The 3-mo acclimation was a legal quarantine that included 1 mo of monitoring for tuberculosis, Shigella, and Yersinia, changes in body weight, and general observation, plus 2 mo of blood chemistry and hematology examination. The sequestered animal room was maintained at a temperature of 23 ± 3°C and relative humidity of 55 ± 10%, with air ventilation of 10 to 20 times/h and a light intensity of 150 to 300 lux with a 12-h light/dark cycle (8 a.m. to 8 p.m.). HEPA-filtered clean air was supplied to the animal room. Throughout the study, the monkeys were housed individually in stainless-steel wire cages (660 W × 800 L × 850 H mm) and fed a standard monkey diet (Oriental Yeast Co., Tokyo). Ultraviolet (UV)-irradiated and filtered municipal tap water was provided to the animals ad libitum. All the animals used in this study were cared for in accordance with the principles outlined in the Guide for the Care and Use of Laboratory Animals, an NRC publication (1996). All experimental protocols were approved by the Animal Care and Use Committee of the Korea Institute of Toxicology. The monkeys were randomly assigned to 3 groups (unexposed 2, low dose 2, and high dose 2) using the Path/Tox System (Version 4.2.2, Xybion Medical Systems Corporation, USA), and exposed to welding fumes for 2 h/day (1:30 p.m.–3:30 p.m.) in the exposure chambers. Before the initiation of inhalation exposure, the monkeys were taken out of their individual cages and housed in individual wire cages (450 W × 600 L × 460 H mm) that were designed for the inhalation experiment. All together, 4 monkeys—2 monkeys in each chamber—were concurrently exposed during each the 2-h exposure period concurrently. Food and water were not provided during the 2 h of exposure. The

FIG. 1. Diagram of welding fume generation system.
monkeys were taken out of the chambers at the end of the 2-h exposure. Blood samples were taken from a vein every 2 wk using a heparin-containing vacutainer and analyzed for the hematology and blood metal concentrations, including Mn, Fe, and Cr. The time-weighted average (TWA) concentrations in the exposure doses were 31.4 ± 2.8 mg/m³ (low dose) and 62.5 ± 2.7 mg/m³ (high dose) total suspended particulate per 2 h. The target concentrations were achieved by varying the flow rates based on adjusting the dampers. The doses were selected based on previous studies conducted with Sprague-Dawley rats, where no distinguishable lung fibrosis was detected after 90 days of welding-fume exposure (Yu et al., 2001, 2003b; Sung et al., 2004). More than 90% of the fume particles had aerodynamic diameters of less than 1 µm, and 50% of the diameters were between 0.65 and 0.43 µm (see Table 2), similar to the previous study (Yu et al., 2001).

**Blood Metal Concentration Analysis**

The Mn and Fe concentrations in the whole blood were analyzed using a Zeeman-corrected flameless (Perkin Elmer 5100ZL Zeeman furnace module, Shelton, CT) atomic absorption spectrophotometer (Perkin-Elmer Analyst 600, Shelton, CT) after sample dilution with a 2% Triton X-100 solution (Mn, Cr) or 2% Triton X-100 solution including 2% ammonium phosphate (Pb, Cd). The metal concentrations were then determined using a flame or flameless method after wet digestion using a microwave digestion system (MDS-2000, CEM, Matthews, NC).

**MRI Imaging**

The monkeys exposed to the welding fumes underwent MRI imaging every month, where the monkeys were anesthetized with ketamine and scanned for 30 min. When the longitudinal magnetization recovers approximately 63% of its final value, this time is known as the T1 relaxation time and is tissue concentration dependent. The T1 relaxation time was measured at 500, 1000, 2000, 4000, and 9000 ms, and the MR scans were performed with a quadrature head coil on a 1.5-T whole-body Siemens SONATA system (Siemens Medical Systems, Erlangen, Germany), which permitted maximum gradient amplitudes of 40 mT/m and a slow rate of 200 mT/m/s. For the T1 calculation, turbo spin echo sequences with different repetition times (TRs) and the same echo time (TE) were used. One slice image was also taken to avoid any slice-cross artifacts in the axial plane. To verify the accuracy of this program, calculations were performed using 7 normal human brains, which resulted in a 5% error.

**RESULTS**

**Distribution of Welding Fume Particles and Concentrations of Total Suspended Particulate During 2 h of Welding-Fume Exposure**

The aerodynamic diameters of the welding fume particles are shown in Table 1. The mean diameter of the particles and the geometric standard deviation were 0.58 µm and 1.49, respectively. The total fume concentrations measured every 15 min showed the exposure system maintained constant concentrations during the 2-h exposure period (Figure 2).

**Concentrations of MMA-SS Welding-Fume Components**

The MMA-SS welding fumes consisted of mainly Fe, Mn, Cr, and Ni. The metal concentrations and gaseous fractions in the welding fumes are shown in Table 2.

**Blood Concentrations of Mn, Cr, and Fe**

The blood manganese concentration increased slightly after 60 days of exposure, and significant increases were observed after 90 days of exposure and reached a plateau thereafter (Figure 3). In contrast, clear increases were observed in the Cr concentration after exposure, and this increase continued until 120 days of exposure (Figure 4). The Fe concentration was not different among the dose groups (Figure 5).

![FIG. 2. Concentrations of total suspended particulate during 2 h of welding-fume exposure.](image-url)
TABLE 2
Concentrations of MMA-SS welding-fume components

<table>
<thead>
<tr>
<th>Metal</th>
<th>Low dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/m³</td>
<td>mg/m³</td>
</tr>
<tr>
<td>Fe</td>
<td>1.84 ± 0.2</td>
<td>3.99 ± 0.5</td>
</tr>
<tr>
<td>Cr</td>
<td>1.41 ± 0.2</td>
<td>3.03 ± 0.3</td>
</tr>
<tr>
<td>Mn</td>
<td>0.90 ± 0.1</td>
<td>1.95 ± 0.2</td>
</tr>
<tr>
<td>Ni</td>
<td>0.15 ± 0.02</td>
<td>0.34 ± 0.1</td>
</tr>
<tr>
<td>Gas</td>
<td>ppm</td>
<td>ppm</td>
</tr>
<tr>
<td>O₃</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>NO₂</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Nitrous fumes</td>
<td>3.8</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Changes in T1 Relaxation Time

The MRI scanning conducted on the basal ganglia region of the primate brains revealed a shortening of the T1 relaxation time after 30 days of welding-fume exposure, and this decrease continued until 90 days, then maintained a plateau up to 180 days (Figure 6).

DISCUSSION

The results of this study clearly indicate that prolonged exposure to welding fumes induces a shortening of the MRI T1 relaxation time, as seen within Mn exposure. Although the tissue Mn content in the brain has already been directly measured in rat brains (Gallez et al., 2001), and indirectly measured in occupationally manganese-exposed welders (Choi et al., 2006) based on the T1 relaxation time, the Mn content in the brain of primates exposed to welding fumes for a prolonged period has never been evaluated. In primates administrated Mn either by inhalation or intravenously, Mn was found to accumulate in the caudate and lenticular nuclei, the substantia nigra, the subthalamic nucleus, the ventromedial hypothalamus, and the pituitary gland (Newland et al., 1989). The shortening of T1-weighted signals persisted in the globus pallidus. Saleem et al. (2002) reported that the striatum and globus pallidus are the initial sites of Mn intoxication in nonhuman primates, based on MRI scanning. Plus, the T1-weighted images have already been used in evaluating Mn exposure in welders. In a study of 121 male workers, including Mn-exposed welders, nonexposed manual workers, and nonexposed clerical workers, it was suggested that the increases of the signal intensities in the T1-weighted images reflect recent exposure to Mn, and the pallidal index (PI, the ratio of the signal intensity of globus pallidus to subcortical frontal white matter) correlates with the blood Mn concentration (Kim et al., 1999). Furthermore, it has been further suggested that an increase in the PI could be used to document increases in the brain Mn level prior to the onset of the clinical symptoms of manganism (Kim et al., 1999; Dietz et al., 2000). However, a direct experimental animal model exposed to welding fumes never has been used to identify the relationship between the welding-fume exposure and the MRI T1 intensity or tissue manganese concentrations at the target sites in the brain. A previous study by the present authors using rats only provided only limited information on the tissue Mn concentrations in the brain after prolonged welding-fume inhalation, and was also limited by the species difference and difficulty of in using of MRI with rats. In contrast, the current welding-fume exposure study on nonhuman primates provides new information regarding the MRI T1 signal intensity along with the blood manganese level.

First, the present study, along with previous studies, suggested that blood manganese concentration is not an effective

FIG. 3. Mn concentrations in blood during 180 days of welding-fume exposure.
short-term exposure biomarker for either both manganese-only exposure or welding-fume exposure (St-Pierre et al., 2001; Vitarella et al., 2000; Dorman et al., 2001, 2006), but rather is a long-term exposure biomarker for welding-fume exposure. Several previous inhalation studies, along with the current study, have found blood manganese concentration to be a poor biomarker for manganese inhalation exposure. The poor correlation between the air and blood manganese concentration may be related to the short half-life of manganese in the blood following acute inhalation exposure (Smargiassi & Mutti, 1999) or intraperitoneal injection (Dastur et al., 1969). In the case of manganese sulfate inhalation in rats, 14 days of repeated exposure

FIG. 4. Cr concentration in blood during 180 days of welding-fume exposure. Since the concentrations for unexposed 1 and 2 were so minute and only showed a small difference, it is difficult to plot the respective symbols differentially.

FIG. 5. Fe concentration in blood during 180 days of welding-fume exposure.
at 3 mg/m$^3$ was insufficient to induce an increase in the blood manganese level (Dorman et al., 2001), yet for rhesus monkeys, 33 days and 65 days of repeated exposure at 1.5 mg/m$^3$ was sufficient to induce an increase in the blood manganese level, which still remained 45 days after the cessation of the subchronic inhalation (Dorman et al., 2006). The present study also indicated that an exposure period of at least 60 days was required to build up a distinguishable blood Mn concentration. Thus, the correlation between the blood manganese concentration and manganese exposure concentration would seem to depend on the magnitude and duration of exposure.

Second, the shortening of the MRI T1 relaxation time, indicative of a high signal intensity in the T1-weighted MRI, can be an effective good biomarker for Mn exposure after short-term welding-fume exposure. As seen in the present results, the MRI changes (in three out of four monkeys) clearly precede the Mn blood rise. The increase of the signal intensities in the T1-weighted images from welders has already been suggested for reflecting recent exposure to Mn (Kim et al., 1999). The concentration of Mn required to produce an increased signal intensity in a T1-weighted MRI is much lower than the threshold necessary to produce overt clinical signs of manganese (Kim, 2002). The T1 relaxation times in the present study decreased time-dependently after exposure, and a visually detectable high signal intensity appeared after 150 days of exposure. The plateau for the shortening of the T1 relaxation time corresponded well with the blood manganese concentration, as previously shown in welders (Choi et al., 2006), suggesting a correlation between a prolonged high manganese concentration in the blood and a shortening of the T1 relaxation time.

Third, the present data strongly suggest that the presence of certain amounts of iron or other metals, such as Cr and Ni, in inhaled welding fumes may not have significant effect on the uptake of Mn into the brain or the induction of a high MRI T1 signal intensity in the basal ganglia. Previous studies on the competition between Fe and Mn for common transporters to cross the blood–brain barrier using cultured cells and rats have indicated that the Mn$^{2+}$ uptake was positively correlated with the pH, suggesting mediation by an electromotive force. The Mn$^{2+}$ uptake was not inhibited by iron or the absence of divalent metal transporter 1 (DMT-1) expression, suggesting an iron transport-independent mechanism (Yokel et al., 2003; Crossgrove & Yokel, 2004). Mn can enter the brain as a complex with transferrin (Tf) via endocytosis, which is mediated by the Tf receptor (TIR) (Aschner & Aschner 1990; Aschner & Gannon, 1994), but the role of TIR-mediated endocytosis in the brain uptake of brain Mn uptake may be minor (Takeda et al., 2000; Malecki, 2001). Mn$^{2+}$ that is not bound to protein enters the brain so much more rapidly than Mn$^{3+}$Tf that even if it were only 1% of total plasma Mn, it can still be the predominant species entering the brain from plasma (Murphy et al., 1991). Tf does not play a major role in the Mn efflux from the brain to the blood (Bradbury, 1997). The concentration of Tf in the brain extracellular fluid is less than 0.25 µmol. If Tf metal-binding sites are occupied by iron, this leaves them unavailable for Mn binding. Thus, a lack of Mn binding sites on Tf in the brain extracellular fluid suggests that TIR-mediated endocytosis may not contribute to the brain-to-blood Mn transfer.
The dietary manganese intake does not affect the brain manganese concentrations following tetroxide or manganese sulfate inhalation in rats maintained on either a manganese-deficient or high-manganese diet (Au: Dorman et al., 2001, 2002). The oral intake of manganese also does not have an affect on the brain manganese concentrations in the current welding-fume inhalation study. Moreover, Kim et al. (2005) observed that blood manganese concentrations are elevated in iron-deficiency anemia patients, while the globus pallidus MRI T1 signal intensity is minimally affected. An unpublished study by the present authors on the welding-fume exposure of iron-deficient rats also showed that there are no significant increases in the manganese concentrations in their brain regions. Thus, when taken together, these data support the notion that the presence of a certain amount of iron in inhaled welding fumes may not have any effect on the Mn uptake into the brain.

REFERENCES


