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3 # Effects of Neonatal Dietary Manganese Exposure
4 on Brain Dopamine Levels and Neurocognitive
5 Functions

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Abstract

16 *Neonatal exposure to high levels of manganese (Mn) has been indirectly implicated as a causal agent in attention*
17 *deficit hyperactivity disorder (ADHD), since Mn toxicity and ADHD both involve dysfunction in brain dopamine (DA)*
18 *systems. This study was undertaken to examine this putative relationship in an animal model by determining if levels of*
19 *neonatal dietary Mn exposure were related to brain DA levels and/or behavioral tests of executive function (EF) when*
20 *the animals reached maturity. We used 32 newborn male Sprague–Dawley rats and randomly assigned them to one of*
21 *the four dietary Mn supplementation conditions: 0, 50, 250 and 500 μg per day, administered daily in water from post-*
22 *natal days 1–21. During days 50–64, the animals were given a burrowing detour test and a passive avoidance test. At*
23 *day 65, the animals were killed and brains were assayed for DA. There was a statistically significant relationship*
24 *($P = 0.003$) between dietary Mn exposure and striatal DA. On the burrowing detour and passive avoidance, greater*
25 *deficits were observed for animals subjected to higher Mn exposure, but these differences did not reach statistical*
26 *significance. However, tests for heterogeneity of variance between groups were statistically significant for all measures,*
27 *with positive relationship between Mn exposure and degree of within-group behavioral variability. Kendall's non-*
28 *parametric test of the relationship between the three behavioral measures and striatal DA levels was also statistically*
29 *significant ($P = 0.02$). These results lend support to the hypothesis that neonatal Mn exposure is related to brain DA*
30 *levels and neurocognitive deficit in the rodent.* © *2002 Published by Elsevier Science Inc.*

31 **Keywords: Dopamine; Behavior; Trace minerals; Manganese; Infant**

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INTRODUCTION

34 There have been persistent reports that children with
35 learning and attention deficits have elevated levels of
36 Mn in their head hair (Pihl and Parks, 1977; Collip
37 et al., 1983; Marlowe and Bliss, 1993). We recently
38 replicated this finding in a well-characterized group of
39 children with attention deficit hyperactivity disorder
40 (ADHD; Crinella et al., 1997). However, the reason for
41 these findings is still unclear.

42 Mn toxicity from industrial exposure has long been
43 known to result in a clinical syndrome, "manganism,"
44 a Parkinson-like condition that provides evidence that
45 Mn is specifically toxic to the brain's dopamine (DA)
46 systems (Donaldson and Barbeau, 1995). ADHD has
47 also been linked to impaired DAergic functioning, so it
48 is feasible that higher levels of Mn in ADHD children
49 is a reflection of a similar neurotoxic insult. However,
50 prevalence of ADHD has not been linked to environ-
51 ments with elevated levels of ambient Mn. In fact, the
52 prevalence rates for the disorder remains constant

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(about 3–5%) across countries where there is a wide variation in ambient Mn exposure (Swanson et al., 1998a,b).

The major source of Mn for all mammalian species is diet, and variations in diet have been shown to increase Mn in tissues, depending on the age of the animal at the time of exposure. The risk of Mn to the neonate has been the topic of several studies (Keen et al., 1994; Bell et al., 1989; Keen et al., 1986; Lönnerdal et al., 1983, 1985; Lönnerdal, 1994). Breast milk has low levels of Mn, but the newborn infant still absorbs Mn in adequate amounts because Mn homeostasis develops slowly in neonatal life. Thus, while Mn absorption is generally high in the first few weeks of life, it shows a steady decrease with age. By the time of weaning, Mn binding in tissues has diminished and/or the excretion mechanism for Mn via bile has become more efficient. As with other organ systems, Mn enters the neonatal brain at a much higher rate than in the adult brain. Neonates are, therefore, at considerable risk of neurotoxicity upon exposure to excess Mn (Kirchgessner et al., 1981).

Formula-fed infants ingest considerably more Mn than breast-fed infants. Lönnerdal (1994) has emphasized the possible clinical significance of the high Mn content in commercial infant formulas, especially those that are soy-based. Breast milk contains 4–6 μg/l, cow's milk formula 30–50 μg/l, and soy formula 200–300 μg/l of Mn. Thus, formula-fed infants may receive as much as 80 times more Mn per day than breast-fed infants, thereby increasing the body burden of Mn, since Mn homeostasis is as yet immature.

Mn concentrations in the blood of formula-fed infants have been shown to be significantly higher than in breast-fed infants (Collip et al., 1983). Since whole blood Mn is an indicator of Mn status, the body burden of Mn in formula fed-infants would be higher than that of breast-fed infants. Animals that are fed even small additional doses of Mn (e.g. 50 μg per day) during the first weeks of life show neuroanatomical damage, including abnormalities in the DAergic nigrostriatal system, with biochemical abnormalities of DA occurring earlier than anatomic lesions (Cawte, 1989).

Neurocognitive deficits

Although many studies have shown that brain tissue and/or neurotransmitter activity can be altered via Mn exposure, there have been few controlled studies of behavioral deficits associated with dietary Mn exposure. In an unpublished report, Penland (1997) showed that rats fed diets that were high in Mn but low in calcium (Ca) showed increased aggressive behavior compared to animals fed other diets. This finding is consistent with studies showing enhanced Mn toxicity in Ca-deficient animals (Murphy et al., 1991).

Studies of rat pups subjected to brain lesions at the time of weaning and tested on a battery of diverse problem solving tasks at maturity (Thompson et al., 1990; Crinella and Yu, 1995, 1999) have shown that the substantia nigra, caudate, putamen, and globus pallidus are critical for optimal performance on every task. It is noteworthy that these nigrostriatal structures are DAergic, and are thus the same structures that are damaged by Mn neurotoxicity.

We have shown that the aforementioned nigrostriatal system is involved in a superordinate cognitive operation that has in recent years been labeled "executive function" (EF). EF deficits are now viewed as the core feature of ADHD (Barkley, 1997). Moreover, brain-imaging studies of children with ADHD are remarkable for the frequency with which differences in nigrostriatal structures (or their phylogenetic extensions) have been found. Not unexpectedly, the presence of anatomical abnormalities in these areas has been associated with favorable clinical response to DA agonists and a DA receptor (D4) gene polymorphism has been found (Swanson et al., 1998a,b).

To explore the potential long-term consequences of early Mn exposure we designed a rat model and evaluated the effects on brain DA and neurocognitive functions.

METHODS

Animals

Pregnant (d14) Sprague–Dawley rats ($n = 12$) were obtained from a commercial source (Charles River Laboratories, Wilmington, MA) and housed in suspended plastic cages throughout the study. Rats were provided rat chow and deionized water ad libitum.

Treatments

One day after delivery, litters were culled to 10–12 pups per dam. Suckling pups were orally gavaged with 25 μl of $MnCl_2$ in 10% sucrose, providing 0, 50, 250, or 500 μg per day from day 1 to 20.

During infancy, and at the time of weaning, 60 pups ($n = 18-24$ per treatment) were killed and tissues

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analyzed for trace elements. In addition, 24 rats were killed at day 35 for DA analysis (the results of which are being reported in a companion study (Tran et al., 2002). The remaining group, consisting of 32 male animals ($n = 8$ per treatment), was fed a purified control diet, with a defined level of Mn (35 μg/g). Behavioral testing began at d50 post-partum, and concluded at d64.

Behavioral methods

Apparatus

Burrowing detour. The precise dimensions of the burrowing detour problem are given in Thompson et al. (1989b). The runway was divided into two sections by a vertical partition, which extended from the top of the apparatus to within 5.8 cm of the floor. The runway in section A sloped downward at 15° from the threshold of the start box, while the floor in section B sloped upward at 15° to the threshold of the goal box. The deepest part of the runway was 5.2 cm below the barrier.

Passive avoidance. The precise dimensions of the passive avoidance box are given in Thompson et al. (1989a). A larger, illuminated compartment was constructed of opaque white Lexan with a transparent Lexan lid. A smaller, dark compartment was constructed of opaque black Lexan and contained a metal grid floor. A guillotine door at one end of the illuminated compartment was open to provide access to the dark compartment. The grid floor was connected to a Variac, which delivered footshocks with an average intensity of 2.8 mA.

Testing procedure

Burrowing detour. Beginning at d50 post-partum, the animal was deprived of water in its home cage for the duration of this experiment. On d52, following 2 days of deprivation, the animal was allowed to explore the apparatus. A dish of water as well as a cup of food (purified diet) was available in the goal box. The animal was allowed to ingest water/food for 10 min, and was then returned to its home cage. From day 53–55, the animal was given 10 preliminary training trials daily, with an intertrial interval of 90–180 s. Each trial began by inserting the rat into the start box and raising the start box door. In most instances, the animal would readily leave the start box, traverse the runway, enter the goal box, and ingest the water and/or mash. After 5 s in the goal box, the animal was carried to a restraining cage to await the next trial. On the 10th trail, the animal was allowed to ingest the water and/or food for approximately 180 s. On d56, the runway was filled with sawdust. In order to gain access to the goal box, the animal was required to burrow under the barrier between sections A and B. Upon entering section A, the start box door was lowered and the animal was allowed 180 s to reach the goal box. If the animal failed to reach the goal box on the first trial, it was transferred to the restraining cage and subsequently given a second test trial after 90–180 s. In the event, the animal succeeded in solving the detour problem on the first or second trial, it was returned to its home cage and given food and water ad lib. If an animal was in the process of tunneling through the sawdust from section A to section B at the end of 180 s, it was allowed to continue as long as it did not return to section A. Animals that failed to solve the problem after receiving two test trials were first placed in the goal box, permitted to ingest the rewards for 5 s, and subsequently given a training trial in which the sawdust was partially displaced from the center of the runway, allowing a space for the animal to pass under the barrier without burrowing. Upon reaching the goal box, the animal was free to ingest the water and/or mash for 10 s and then given a third test trial, with sawdust restored to the level of the start box.

On d56, the time from the moment the animal entered section A to the moment the animal began to dig was recorded (digging latency), as well as the time required for the animal to reach the goal box once digging began (running time).

Passive avoidance. Following a 3-day rest period, during which time the animal was given food and water ad libitum, the animal began a schedule of one trial per day, for five consecutive days (post-partum d60–64), on the passive avoidance problem. The rat was placed in the illuminated compartment, and a trial was initiated by raising of the guillotine door. If the rat entered the dark compartment, i.e. all four paws being beyond the threshold, individual footshocks were administered at a rate of one every 2 s until the rat returned to the illuminated compartment (all four paws being over the threshold). No further footshocks were given unless the animal reentered the dark compartment. The trial was terminated when the animal refrained from entering the dark compartment for 5 min. The animal's score consisted of the total number of footshocks received, over 5 days.

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Biochemical methods

Sample collection

Within 48 h of the last cognitive test, each rat was killed via rapid decapitation. Brains were removed, and striatal tissue was dissected out on an ice-cold glass plate. The isolated tissues were flash frozen on dry ice and stored at −70 °C until assay. DA levels were determined by radioimmunoassay (ALPCO, Windham, NH). Tissues samples were homogenized in 0.1N HCl (10 mg/ml) on ice, and centrifuged for 5 min at 8000–10,000 × *g* until the supernatant was clear. Supernatants were extracted (100 µl sample buffer, 250 µl extraction buffer) on a coated macrotiter plate using a *cis*-diol-specific affinity gel, 60 min at room temperature on an orbital shaker, 600–900 rpm. The bound catecholamines were acylated (250 acylation buffer, 50 µl acylation reagent) for 15 min room temperature on an orbital shaker 600–900 rpm) and eluted with 0.025 M HCl (0.75 µl). Acylated compounds were enzymatically converted into *N*-acyl-3-methoxytryptamine with catechol-*O*-methyltransferase (50 µl, incubation at 37 °C for 60 min) and assayed in duplicate (25 µl per assay tube) by RIA. The aspirated pellets were quantified using a gamma counter (ICN Biomedical, formerly Micromedic, Isoflex Gamma Counter). Results were obtained by interpolation from the standard curve. The minimum detectable dose was approximately 50 pg/ml with a reported intra-assay CV of 8–15% and an inter-assay CV of 6–12%. Tissue protein was measured according to the method of Bradford (1976) using a commercially available Bio-Rad Protein kit. Data reduction for the RIA and IRMA assays was performed by a computer assisted four-parameter logistics program (Rodbard and Hutt, 1974).

Statistical analysis

Graphpad Prism 3.0 and SPSS were used for data analysis. One-way ANOVA followed by Tukey test was used to behavior tests and striatal DA. Regression analysis was used to compare the behavioral test results to striatal DA levels.

RESULTS

Striatal DA concentrations

Fig. 1 shows mean striatal DA levels for each of the four exposure groups. Mean DA levels for controls (1.42 ng/mg) and low exposure (1.60 ng/mg) did not differ significantly, while the medium exposure (0.75 ng/mg) and high exposure (0.58 ng/mg)) groups were dramatically lower, the latter being only 40% of the mean control level. The between-group difference was highly significant ($F = 5.399$; $P = 0.004$).

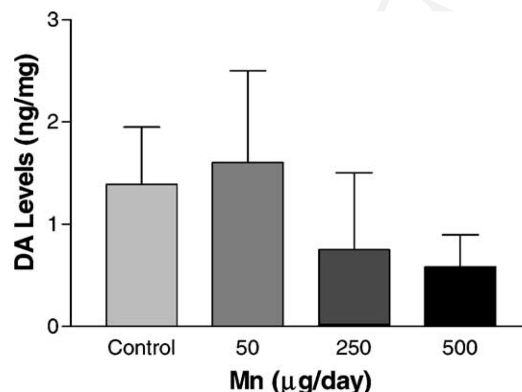

Fig. 1. Striatal dopamine levels for four groups of animals sacrificed at post-natal day 65. Treatment reflects Mn levels in solution, orally-administered form post-natal days 1–21.

Behavioral outcomes

Burrowing detour problem

Fig. 2 shows mean digging latencies, and Fig. 3 shows mean running times for the four exposure groups. As can be seen, there was an apparent trend towards increased latency at higher exposure levels, but the mean differences were not statistically significant ($F = 0.315$; $P = 0.814$). There was also an apparent trend towards increased burrowing completion time at higher exposure levels, but again the mean differences did not reach statistical significance. ($F = 0.262$; $P = 0.852$). However, for both measures, the within-group variances increased rather dramatically for the

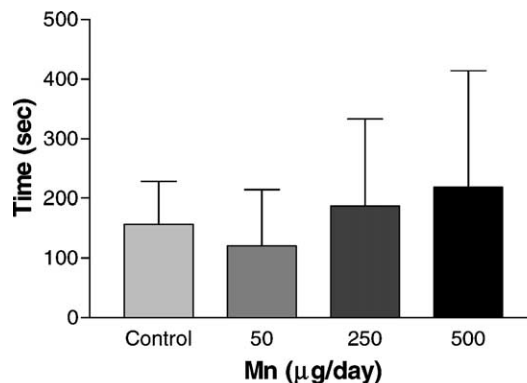

Fig. 2. Digging latency on post-natal day 58 in the burrowing detour problem for four groups of animals. Treatment refers to Mn levels in solution, orally-administered from post-natal days 1–21.

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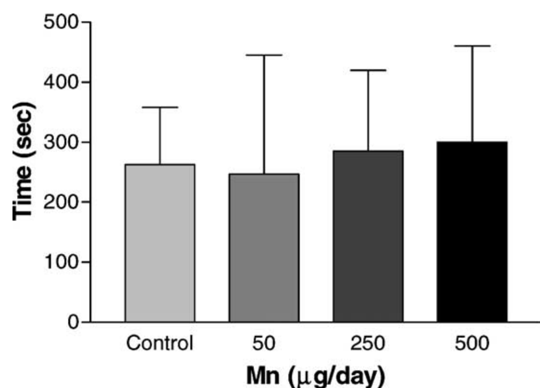

Fig. 3. Running time on post-natal day 58 in the burrowing detour problem for four groups of animals. Treatment refers to Mn levels in solution, orally-administered from post-natal days 1–21.

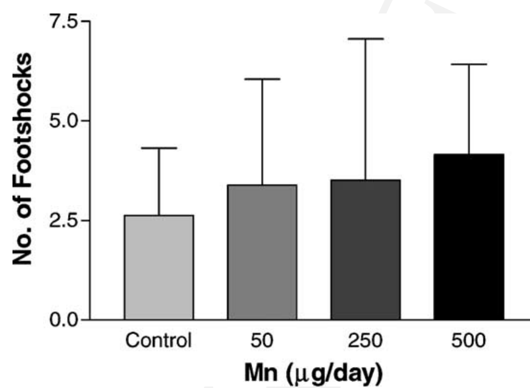

Fig. 4. Total number of footshocks received in the passive avoidance apparatus, over post-natal days 60–64, for four groups of animals. Treatment refers to Mn levels in solution, orally-administered from post-natal days 1–21.

higher exposure levels. Levene's test for equality of error variance was statistically significant for both measures (digging latency, $F = 4.522$, $P = 0.01$; running time, $F = 2.96$, $P = 0.05$). Further, the dramatic rise in variance with increased exposure suggests that there is a treatment effect.

Passive avoidance problem

Fig. 4 shows the mean number of footshocks given in the passive avoidance test over 5 days of testing, for the four exposure groups. As can be seen in the figure, there was an apparent trend for animals that experienced higher Mn exposure to have had greater difficulty with inhibition of the behavior that resulted in a footshock. However, the finding was not statistically significant ($F = 0.443$; $P = 0.74$). As with the burrowing detour problem, the within-group variances were apparently different among the groups, although this finding did not reach significance using Levene's tests ($F = 1.140$; $P = 0.352$).

Concordance among outcome measures

Because the heterogeneity of group variances for the three behavioral measures, a planned multiple regression analysis, using the three behavioral measures to predict DA levels, would not have been legitimate. Because there was a trend for each behavioral measure to be related to exposure level, a non-parametric test of agreement among ranks was used, as shown in Table 1. Kendall's coefficient of concordance (W) among ranks was 0.925, which is statistically significant ($\chi^2 = 11.1$; d.f. $= 3$; $P < 0.02$).

DISCUSSION

In demonstrating a significant relationship between neonatal Mn exposure levels and striatal DA levels at d60, we lend further support to the findings of others who have shown that neurotoxic damage from Mn is characterized by selective injuries to DAergic brain networks (Chandra and Shukla, 1981; Eriksson et al., 1987, 1992). We had additionally hypothesized that neonatal Mn exposure, at levels sufficient to deplete DA in the striatum, would produce deficits in EF, as evidenced by incapacity to perform tests that required response inhibition, mental flexibility, and shifting of cognitive sets.

The connection between Mn exposure level, DA depletion, and EF deficit was difficult to establish because of extensive within-group variance for all

Table 1
Group ordinal rankings on three behavioral measures and on 65 day striatal dopamine levels

Group	Digging latency		Running time		Footshocks		DA level		Sum of ranks
	Mean	Rank	Mean	Rank	Mean	Rank	Mean	Rank	
Control	157	2	262	2	2.63	1	14.24	2	7
50	120	1	246	1	3.38	2	16.02	1	5
250	187	3	285	3	3.50	3	6.77	3	12
500	218	4	300	4	4.14	4	5.83	4	16

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behavioral measures, a phenomenon that appeared itself to be a function of Mn exposure level. This finding of higher within-group variances as a function of exposure levels did, in fact, achieve statistical significance, and is, therefore, of some interest. It suggests a greater likelihood of extreme behavioral deficit as a function of Mn exposure, even though a good proportion of the high and medium Mn exposure animals seemed to have developed adequate performance levels, i.e. not appreciably different from the performances of the control or low exposure animals.

There are several possible reasons for our findings. First, the treatment itself involved rather modest levels of Mn, designed to mimic the dietary exposure of Mn of breast-fed versus formula-fed human infants. Furthermore, ingested amounts may have varied, and some pups may have been more successful than others in suckling, thereby receiving sufficient quantities of nutrients such as iron or calcium from milk, which are known to offer protection against Mn-induced neurotoxicity (Keen et al., 1994; Murphy et al., 1991). The possibility that some animals were incompletely treated is also suggested by the results of our companion study of Mn tissue absorption in these animals (Tran et al., 2002) which found that these same levels of treatment did not cause significant differences in tissue Mn at d40, even though there were significant striatal DA deficits as well as behavioral deficits (passive avoidance) at d32 post-partum. Keen et al. (1994) found that Mn increased in all tissues of exposed animals at day 14, suggesting that there is a developmental window for tissue absorption, but that even when tissue levels are normal there can already be sufficient disruption of DA systems to cause later behavioral deficit.

It is also possible that the behavioral measures used are not optimally sensitive to DA deficits of the type and/or magnitude of those induced in this study. While these behavioral methods have proven sensitive to electrolytic and neurochemical lesions in nigrostriatal and related structures (Thompson et al., 1990), the Mn exposure levels employed in this study were likely to have produced far less destructive lesions. In future studies, this possibility will be investigated by a more comprehensive battery of tests, as well as by histological analysis to directly determine tissue loss in critical brain structures.

The relevance of these results to the human clinical disorder, ADHD, remains unclear. If neonatal exposure to Mn has a causal relationship to an ADHD-like syndrome, a more daunting challenge will be found in the search for an explanation of why neonatal dietary Mn exposure continues to be reflected in the head hair in school-age children with ADHD.

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