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Neurochemical Changes in Rats Chronically Treated with a High Concentration of Manganese Chloride*

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Several neurochemical parameters were studied in brain regions of rats chronically treated with a high concentration of manganese chloride (20 mg $MnCl_2.4H_2O$ per ml. of drinking water) throughout development until adulthood. Large increases in Mn accumulation were found in all brain regions (hypothalamus, +530%; striatum, +479%; other regions, +152 to +250%) of Mn-treated adult rats. In these animals, Ca levels were decreased (−20 to −46%) in cerebellum, hypothalamus, and cerebral cortex but were increased (+186%) in midbrain. Mg levels were decreased (−12 to −32%) in pons and medulla, midbrain, and cerebellum. Fe levels were increased (+95%) in striatum but were decreased (−28%) in cerebral cortex. Cu levels were increased (+43 to +100%) in pons and medulla and striatum but Zn levels were decreased (−30%) in pons and medulla. Na levels were increased (+22%) in striatum but those of K and Cl remained unchanged. Type A monoamine oxidase activities were decreased (−13 to −16%) in midbrain, striatum, and cerebral cortex, but type B monoamine oxidase activities decreased (−13%) only in hypothalamus. Acetylcholinesterase activities were increased (+20 to +22%) in striatum and cerebellum. The results are consistent with our hypothesis that chronic manganese encephalopathy not only affects brain metabolism of Mn but also that of other metals.

KEY WORDS: Manganese toxicity; neurochemical changes in manganese toxicity; brain regional electrolytes; brain regional trace metals; monoamine oxidase; acetylcholinesterase.

INTRODUCTION

Manganese is a nutritionally required trace element: its deficiency and excess invariably result in altered brain function and behavior (1,2). Although the functional and neurochemical roles of manganese during development have not been fully elucidated, exposure of the mature nervous system to high levels of manganese is known to bring about definite changes in a number of neurochemical markers of neurotransmitter (3-11) and energy metabolism (12,13). However, the neurotoxic effects of chronic and continuous manganese exposure on the developing nervous system have not been extensively investigated (see Ref. 13 for discussion).

In one developmental rat model of chronic manganese encephalopathy (13-15), age-related changes in the markers of the GABAminergic, dopaminergic, and cholinergic systems have been demonstrated (13-17). However, the effects of chronic manganese toxicity upon

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*We dedicate this paper to Professor Alan N. Davison. Professor Davison has conducted pioneering research in several important areas including: brain development and myelination, aging and Alzheimer's disease, and multiple sclerosis. He encouraged us to investigate the neurochemical mechanisms of neurotoxicity of metal ions, particularly in connection with neurological diseases. His encouragement and continued support facilitated the launching of our multidisciplinary research program in the long-term effects of manganese toxicity on brain development and aging.

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some of these neurochemical parameters in the developing brain are, in general, still controversial. For instance, reports regarding such effects on the putative cholinergic marker, acetylcholinesterase (AChE), are conflicting (10,12,13,18-21). Furthermore, some (12,19,22,23) but not all (11,13,24-26) workers reportedly found changes in brain monoamine oxidase (MAO) activities in animals chronically treated with manganese. The contrasting results obtained by various research groups could at least be partially attributed to the differences in the manner and the dose of manganese administration (resulting in dissimilar degrees of brain Mn accumulation in the various animal models) adopted in different studies (see Ref. 27 for discussion). Thus, there is a need to compare and evaluate the effects of manganese toxicity on various neurochemical markers in the same animal model.

Our previous studies have demonstrated that in a developmental rat model of chronic manganese toxicity, the brain regional concentrations of manganese show increases that can be related to the dose of manganese administered (14,27-29). Using this model, we have found that treatment with two concentrations of manganese (1 and 10 mg of $MnCl_2.4H_2O$ per ml. of drinking water) during development did not bring about marked changes in type A (MAO-A) or type B (MAO-B) monoamine oxidase activities in brain (13,24,25) although definite changes in MAO-A and MAO-B activities in peripheral tissues - particularly in liver - of the treated animals were observed (25,30). In another study employing manganese treatment at the same concentrations, we have not detected any pronounced effects on brain regional distribution of AChE during development (20). Since the effects of chronic manganese toxicity on brain MAO and AChE are still controversial (10-13,18-26), the present study was initiated to extend our previous studies (13,14,20,24,25) and to specifically address the following questions. 1) Will treatment at a much higher concentration of manganese (20 mg $MnCl_2.4H_2O$ per ml. of drinking water) using our developmental rat model of chronic manganese encephalopathy (13,14) result in even higher accumulation of this metal in various brain regions? 2) If (1) were true, will the effects of manganese treatment (at this much higher concentration) on brain MAO and AChE activities be different from those of treatment at the lower concentrations (1 or 10 mg $MnCl_2.4H_2O$ per ml. of drinking water)? 3) Will chronic manganese toxicity which gives rise to increased brain accumulation of manganese affect brain metabolism of other trace metals and electrolytes since evidence is accumulating that metals interact with one another in their uptake and metabolism?

EXPERIMENTAL PROCEDURE

Materials. 5-Hydroxy-2-[^{14}C]tryptamine creatinine sulfate (specific activity = 58 mCi/mmol) and 7-[^{14}C]benzylamine hydrochloride (specific activity = 56 mCi/mmol) were from the Radiochemical Centre, Amersham, U.K. All other chemicals were of analytical (AR) grade and obtained either from BDH Chemicals Ltd., Enfield, Middlesex, U.K., or Sigma (London) Ltd., Poole, Dorset, U.K. Solutions were prepared using deionized glass-distilled water.

The Developmental Rat Model of Chronic Manganese Encephalopathy. Wistar rats (M.R.C. Porton strain) were used in all experiments. The details of this model have been published elsewhere (13-16). In essence, rats were exposed to manganese (20 mg $MnCl_2.4H_2O$ per ml. of drinking water) continuously throughout development till they were used for experiments at adulthood (i.e., 90-day-old males). Thus, in utero, they were exposed to manganese via their mothers' circulation; postnatally, they were exposed to this metal via their mothers' milk (13-16). From around weaning onward, they were directly exposed to manganese which had been included in their drinking water (13-16). Untreated rats matched for age and sex were employed as controls. The age-related increases in body weight in the manganese-treated animals were significantly less than those in control rats (25) although the brain weight:body weight ratios in the two groups did not significantly differ (T.K.C. Leung, J.C.K. Lai, and L. Lim, unpublished data).

Preparation of Brain Homogenates for Enzymatic Assays. Animals were decapitated and their brains rapidly removed and dissected on a Petri-dish on ice according to the procedure of Glowinski and Iversen (31) into six regions: hypothalamus, cerebellum, pons and medulla, striatum, midbrain, and cerebral cortex (which also included the hippocampus). A 10% (w/v) homogenate was prepared as described by Lai et al. (32) except that the medium consisted only of 0.32 M sucrose and 5 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid - KOH, pH 7.4.

Assays of Enzymatic Activities and Protein. Acetylcholinesterase (AChE, EC 3.1.1.7) activity was assayed as described by Lai and Clark (33). Monoamine oxidase (MAO; EC 1.4.3.4) activity was determined as described by Leung et al. (24,25): MAO-A was assayed with ^{14}C-labeled 5-hydroxytryptamine and MAO-B with ^{14}C-labeled benzylamine (24,25). Protein was determined by the method of Lowry et al. (34) with bovine serum albumin as the standard.

Determination of Brain Regional Concentrations of Trace Metals and Electrolytes. Each brain was dissected into regions as described above. The contents of trace elements and electrolytes in freeze-dried samples of brain regions were determined by instrumental neutron activation analysis (INAA). The details regarding this method, its sensitivity and precision, and the detection limits for various elements have been published elsewhere (27,35).

Statistical Analysis. This was carried out using non-paired *t*-test. Only P values less than 0.05 were regarded as significant.

RESULTS

Effects of Chronic Treatment with Manganese Chloride on Brain Regional Distribution of MAO and AChE. In control rats, MAO-A activities were highest in hypothalamus and cerebral cortex, intermediate in midbrain and striatum, but lowest in cerebellum and pons and medulla (Table I). These results are compatible with

those reported previously (13,24). Chronic treatment with manganese throughout development resulted in small but significant ($P < 0.05$) decreases in MAO-A activities in midbrain (−13%), striatum (−15%) and cerebral cortex (−16%) although the relative regional distribution of MAO-A in treated rats was similar to that in control rats (Table I).

The regional distribution of MAO-B activities in control animals is similar to that reported previously (13,24), being highest in hypothalamus, intermediate in cerebellum, midbrain, and cerebral cortex, but lowest in striatum and pons and medulla (Table I). Chronic manganese treatment throughout development gave rise to a decrease in MAO-B activity only in the hypothalamus (−13%; $P < 0.05$) but not an alteration in the relative regional distribution of MAO-B (Table I).

In accord with previous observations (15,20), activities of AChE in control animals were particularly high in striatum but quite low in cerebellum, the values in other regions being about 40 to 50% of those in striatum (Table I). This distribution pattern was not altered by the chronic manganese treatment although enzymatic activities were significantly ($P < 0.05$) increased in striatum (+20%) and cerebellum (+22%) (Table I).

Effects of Chronic Treatment with Manganese Chloride on Brain Regional Distribution of Manganese (Mn), Calcium (Ca), and Magnesium (Mg). Mn concentrations in control animals were lower in striatum than in the other regions; Mn levels did not markedly differ in regions other than striatum (Table II). Chronic Mn treatment throughout development led to marked increases in Mn in all brain regions (Table II). The increased accumulation of Mn was especially pronounced in hypothalamus (+530%; $P < 0.003$) and striatum (+479%; $P < 0.003$). As a result of the treatment-induced increases in brain Mn, the regional Mn distribution in the treated animals was altered, being highest in hypothalamus, intermediate in striatum and midbrain, but lowest in pons and medulla, cerebellum, and cerebral cortex (Table II).

Ca levels in control rats were highest in hypothalamus, cerebellum and pons and medulla, intermediate in striatum and cerebral cortex, but lowest in midbrain (Table II). These findings confirm that the distribution of brain Ca is uneven in this (35) and other (36,39) species. Chronic Mn treatment throughout development gave rise to significant decreases in Ca in cerebellum (−46%; $P < 0.01$), hypothalamus (−26%; $P < 0.05$) and cerebral cortex (−20%; $P < 0.05$) but increases in midbrain (+186%; $P < 0.01$) (Table II). Consequently, the brain regional Ca distribution was also severely altered in the treated rats (Table II), being highest in pons and medulla, hypothalamus and striatum, intermediate in midbrain, but lowest in cerebral cortex and cerebellum.

In control rats, Mg concentrations were lower in cerebral cortex than in the other regions (Table II). Chronic Mn treatment throughout development significantly altered regional Mg distribution (Table II) by decreasing Mg accumulation in pons and medulla (−32%; $P < 0.05$), midbrain (−24%; $P < 0.05$), and cerebellum (−12%; $P < 0.05$).

Effects of Chronic Treatment with Manganese Chloride on Brain Regional Distribution of Iron (Fe), Copper (Cu), and Zinc (Zn). In accord with our previous findings (35), brain Fe concentrations in control rats were higher in pons and medulla, hypothalamus and cerebellum than in striatum and cerebral cortex (Table III).

Chronic Mn treatment throughout development led to significant increases in Fe concentration in striatum (+95%; $P < 0.01$) but decreases in Fe concentration in cerebral cortex (−28%; $P < 0.05$) (Table III).

Cu levels in control rats were highest in hypothalamus but lowest in pons and medulla and cerebral cortex, the levels in the other regions being in between the two extremes (Table III). This regional distribution is

Table I. Effects of Chronic Manganese Treatment on Brain Regional Distribution of Type A (MAO-A) and Type B (MAO-B) Monoamine Oxidase and Acetylcholinesterase Activities

Enzyme	Treatment	HY	CB	PM	ST	MB	CC
MAO-A	Control	2.00 ± 0.04	1.20 ± 0.18	1.10 ± 0.03	1.46 ± 0.04	1.51 ± 0.05	1.73 ± 0.17
	Mn-treated	1.81 ± 0.19	1.04 ± 0.12	1.17 ± 0.13	1.24 ± 0.04**	1.32 ± 0.10*	1.45 ± 0.03*
MAO-B	Control	0.86 ± 0.02	0.63 ± 0.14	0.47 ± 0.05	0.55 ± 0.08	0.63 ± 0.12	0.63 ± 0.05
	Mn-treated	0.75 ± 0.04*	0.61 ± 0.10	0.48 ± 0.03	0.48 ± 0.05	0.54 ± 0.06	0.55 ± 0.05
AChE	Control	77.1 ± 2.1	22.4 ± 2.4	64.5 ± 4.1	176.0 ± 11.1	80.6 ± 8.3	70.9 ± 5.7
	Mn-treated	77.5 ± 2.8	27.3 ± 2.4*	72.3 ± 6.1	210.5 ± 19.7*	84.9 ± 7.7	72.4 ± 3.6

The abbreviations are: HY, hypothalamus; CB, cerebellum; PM, pons and medulla; ST, striatum; MB, midbrain; CC, cerebral cortex; and n, number of animals used. Values are specific activities (in nmol/min/mg protein) and are given as means ± SD ($n = 6$). *$P < 0.05$, and **$P < 0.01$ versus corresponding control values. Other details are the same as those described in Experimental Procedure.

Table II. Effects of Chronic Manganese Treatment on Brain Regional Distribution of Manganese (Mn), Calcium (Ca), and Magnesium (Mg)

Metal	Treatment	HY	CB	PM	ST	MB	CC
Mn	Control	0.30 ± 0.13	0.38 ± 0.05	0.37 ± 0.12	0.24 ± 0.03	0.38 ± 0.01	0.34 ± 0.07
	Mn-treated	1.89 ± 0.12+	1.04 ± 0.10+	1.12 ± 0.10+	1.39 ± 0.24+	1.33 ± 0.20+	0.83 ± 0.16+
Ca	Control	137 ± 28	109 ± 9	104 ± 7	78 ± 9	29 ± 13	76 ± 2
	Mn-treated	102 ± 1*	59 ± 8**	111 ± 3	98 ± 22	83 ± 24**	61 ± 7*
Mg	Control	236 ± 91	221 ± 23	263 ± 33	225 ± 41	267 ± 26	154 ± 39
	Mn-treated	248 ± 151	194 ± 5*	179 ± 30*	228 ± 38	202 ± 34*	181 ± 24

Values are in μg/g wet weight and are given as means ± SD (n = 6). *P< 0.05, **P< 0.01, +P< 0.003 versus corresponding control values. The other details are the same as those in the Legend to Table I.

Table III. Effects of Chronic Manganese Treatment on Brain Regional Distribution of Iron (Fe), Copper (Cu), and Zinc (Zn)

Metal	Treatment	HY	CB	PM	ST	MB	CC
Fe	Control	29 ± 11	27 ± 8	29 ± 6	19 ± 5	23 ± 4	18 ± 2
	Mn-treated	40 ± 9	29 ± 10	25 ± 6	37 ± 8**	25 ± 5	13 ± 2*
Cu	Control	13 ± 1	6 ± 2	4 ± 2	7 ± 1	6 ± 2	3 ± 1
	Mn-treated	12 ± 1	6 ± 0	8 ± 1**	10 ± 1**	8 ± 1	4 ± 0
Zn	Control	12 ± 1	11 ± 2	10 ± 2	11 ± 2	10 ± 1	14 ± 1
	Mn-treated	12 ± 3	11 ± 1	7 ± 1*	11 ± 2	10 ± 1	14 ± 2

Values are in μg/g wet weight and are given as means ± SD (n = 6). The other details are the same as those in the Legend to Table II.

similar to those reported previously (35,37,38,40). Chronic Mn treatment throughout development resulted in significant increases in Cu accumulation in pons and medulla (+100%; P< 0.01) and striatum (+43%; P< 0.01) (Table III).

The regional variation in Zn concentration was not marked in control rats, being slightly higher in cerebral cortex but marginally lower in pons and medulla and midbrain (Table III). These results are compatible with those in the literature (35,37,38,40). Moreover, the regional distribution of Zn was not affected by the Mn treatment although Zn levels in pons and medulla (−30%; P< 0.05) of treated animals were decreased (Table III).

Effects of Chronic Treatment with Manganese Chloride on Brain Regional Distribution of Sodium (Na), Potassium (K), and Chloride (Cl). In control rats, the brain regional variations of Na, K, and Cl were small, the levels of these elements being marginally higher in pons and medulla but lower in hypothalamus (Table IV). These data are compatible with those in the literature (35-39,41). Chronic Mn treatment throughout development only gave rise to a small increase (+22%; P< 0.05) in Na level in striatum (Table IV). On the other hand, this Mn-treatment did not lead to significant changes either in brain K levels or in brain Cl levels (Table IV).

DISCUSSION

Since evidence is accumulating that metals interact with each other in their tissue uptake and metabolism (see Ref. 27 for a discussion), we have hypothesized that excess intake of one metal, be it essential or otherwise, alters the brain metabolism of this and other metals (14,27,28). The studies reported in this paper constitute the first reported attempt to elucidate the effects of chronic exposure of the developing brain to a high concentration of Mn on brain metabolism of Mn, other trace metals, and electrolytes. We have developed a sensitive technique of instrumental neutron activation analysis (INAA) to specifically address this issue and have elaborated on the relative merits of INAA elsewhere (27,35).

Although brain levels of metals in both humans (see Ref. 42 for a discussion) and experimental animals (14,27,28,36-41) have been known to show regional variations, very few studies on Mn encephalopathy re-

Table IV. Effects of Chronic Manganese Treatment on Brain Regional Distribution of Sodium (Na), Potassium (K), and Chloride (Cl)

Electrolyte	Treatment	HY	CB	PM	ST	MB	CC
Na	Control	800 ± 230	930 ± 150	1080 ± 90	860 ± 140	930 ± 90	860 ± 60
	Mn-treated	1050 ± 70	1030 ± 30	1080 ± 150	1050 ± 40*	1140 ± 180	910 ± 20
K	Control	3480 ± 810	4180 ± 560	4230 ± 480	3980 ± 710	3670 ± 440	3960 ± 340
	Mn-treated	4210 ± 360	4120 ± 250	3850 ± 540	4490 ± 280	4130 ± 440	3720 ± 280
Cl	Control	870 ± 230	910 ± 180	1140 ± 130	920 ± 130	960 ± 130	790 ± 120
	Mn-treated	1110 ± 60	980 ± 20	1080 ± 150	1060 ± 40	1140 ± 180	910 ± 30

Values are in μg/g wet weight and are given as means ± SD (n = 6). The other details are the same as those in the Legend to Table II.

port brain regional Mn levels (see Refs. 14, 27 and 38 for discussion). Thus, it has not been possible to relate the neurochemical, morphological, neuropharmacological and behavioral changes in experimental Mn encephalopathy to the changes in brain regional Mn levels resulting from the Mn treatment if, indeed, such changes in Mn levels occur. Although the actual Mn levels in the various rat brain regions reported by different workers (14,22,27-29,35,37,38) are not identical (presumably because of dissimilar analytical techniques, strains of rats, and rat diets employed), most workers agree that Mn levels are higher in midbrain, cerebellum, and hypothalamus but lower in striatum (14,22,27-29,35,37,38).

Our initial studies on experimental Mn encephalopathy in the rat demonstrate that chronic exposure of the developing brain to Mn (1 or 10 mg $MnCl_2.4H_2O$ per ml. of drinking water) alters the brain regional distribution of Mn (14,28). We find that the Mn levels in rats treated with a much higher concentration of Mn (20 mg $MnCl_2.4H_2O$ per ml. of drinking water) were highest in hypothalamus, striatum and midbrain, but lowest in cerebellum and cerebral cortex (Table II). Furthermore, in these animals, very marked increases in Mn accumulation occurred in hypothalamus (+530%) and striatum (+479%) although significant increases in Mn accumulation (+100 to +300%) also occurred in the other regions (Table II). Similarly, Deskin and coworkers (22) observed large increases in Mn accumulation in the only two regions (i.e., hypothalamus and corpus striatum) they had reportedly studied in neonatal rats treated with Mn (1-20 mg/Kg body weight/day) by oral gavage for 24 days. By contrast, intraperitoneal administration of Mn (3 mg/Kg body weight/day) to adult rats for 30 days gave rise to large increases in Mn accumulation in corpus callosum (+1300%), corpus striatum (> +300%), thalamus and amygdala; however, the increased Mn accumulation in hypothalamus (< +50%) was not as remarkable (38). Viewed together, our own (14,27-29) and other (22,38) observations suggest that different routes of Mn administration can result in dissimilar but region-selective increases in brain Mn accumulation.

Chronic exposure of the developing brain to a high concentration of Mn has pronounced but selective effects on brain regional metabolism of several trace metals and electrolytes in addition to Mn. Of these, the most marked are the effects on brain regional distributions of Ca and Mg (Table II). This is hardly surprising since Mn can interact with both Ca and Mg in a number of processes in the transport and metabolism of Ca and Mg (see 27 for discussion and Refs.). The effect on Ca is unexpectedly biphasic in that Ca level in midbrain only was increased (+186%) whereas levels in cerebellum (−46%), hypothalamus (−26%) and cerebral cortex (−20%) were decreased (Table II). Ca levels in striatum and pons and medulla also showed a tendency to increase although the increases were not statistically significant ($P > 0.05$; Table II). Mg levels were significantly decreases in pons and medulla (−32%), midbrain (−24%), and cerebellum (−12%) (Table II). Bearing in mind that Scheuhammer and Cherian (38) employed a different model of Mn encephalopathy and route of Mn administration, their results are interesting in that they also found small decreases in Mg levels in midbrain and hypothalamus in their Mn-treated rats; however, these workers (38) reported a small but significant increase in Mg in corpus callosum. Scheuhammer and Cherian (38) did not reportedly study the Mn-induced effects on brain Ca.

Unlike the Mn-induced effects on Ca and Mg (Table II), the effects on the trace metals are less pronounced but nevertheless highly region-specific (Table III). Chronic Mn exposure during brain development led to changes in Fe accumulation only in striatum (+95%) and cerebral cortex (−28%) - a large increase in the former but a decrease in the latter (Table III). In the treated animals, the only significant changes in Zn levels was a decrease (−30%) in pons and medulla (Table III). Our

results contrast with those of Scheuhammer and Cherian (38) who did not detect any changes in brain Fe levels in their Mn-treated animals but reported increases in brain Cu levels in most of the regions they had studied with the exception of olfactory bulb, midbrain, colliculi and hypothalamus. Unlike our data (Table III), Scheuhammer and Cherian (38) reported small decreases in Zn levels in amygdala and hypothalamus but not in other brain regions of adult rats treated intraperitoneally with Mn.

Chronic manganese toxicity in adult rats can induce changes in brain Na and K metabolism (27,38). Scheuhammer and Cherian (38) reported that K levels were decreased in corpus striatum, midbrain, colliculi, and corpus callosum but Na levels were increased in amygdala and olfactory bulb and decreased in corpus striatum and midbrain in adult rats treated with Mn. By contrast, chronic exposure of the developing brain to a high concentration of Mn induced a small increase in Na level only in striatum but did not result in significant changes in regional levels of K or Cl (Table IV). Thus, it is possible (and likely) that Mn, administered via different routes, may exert dissimilar effects on brain metabolism of metals and electrolytes.

Whether or not Mn toxicity has any effects on brain neurotransmitter-metabolizing enzymes remains a controversial issue. In early studies, Chandra and coworkers (12,19) detected increased brain activities of MAO in Mn-treated animals whereas in more recent studies (23) they reported that striatal MAO activities were only increased during the initial phase of chronic Mn treatment. On the other hand, other workers have found that brain MAO activities in Mn-treated animals show both increases and decreases (22), or remain unchanged (11,13,24-26). Since MAO in brain and other tissues is known to exist in at least two forms (see Ref. 24 for a full discussion) and none of the studies discussed (11,12,19,22,23,26) were designed to address the Mn-induced effects on the heterogeneity of brain MAO, it is not surprising that these reported effects of Mn toxicity on brain MAO (11,12,19,22,23,26) are contradictory.

We initiated a series of studies to specifically resolve the issue of the putative Mn-induced effects on the heterogeneity of MAO using specific substrates and inhibitors (see Refs. 13 and 24 for a full discussion). In previous studies with our developmental rat model of chronic Mn encephalopathy, MAO-A (serotonin-oxidizing) activity was found to be slightly increased (+13%) only in cerebellum whereas MAO-B (benzylamine-oxidizing) activity in various regions remain unchanged (24). More recently, we have studied the age-related increases in brain MAO-A and MAO-B activities in the treated rats and found them to be very similar to those in control animals (24). Even chronically exposing the developing animals to a much higher concentration (20 mg $MnCl_2.4H_2O$ per ml. of drinking water) only results in small decreases in MAO-A activity in striatum (−15%), midbrain (−13%), and cerebral cortex (−16%) and a small decrease (−13%) in MAO-B activity only in hypothalamus (Table I).

Similar to MAO, the Mn-induced effect on brain AChE activity has also been a controversial issue. Whereas Chandra and associates have reported chronic Mn-treatment either decreased (12,18) or did not alter (19) the activity of this enzyme, other workers (13,15,20,21) - including ourselves (20; Table I) - agree that such a treatment produces little, if any, effect on its activity. Thus, our results (13,20,24,25; Table I), taken together, suggest that AChE, MAO-A and MAO-B in brain are rather insensitive to the chronic Mn insult.

In conclusion, the results of this paper provide some support for our hypothesis that chronic Mn encephalopathy affects the brain metabolism of not only Mn but also that of other trace metals (e.g., Cu, Fe, Zn) and electrolytes (e.g., Ca, Mg, Na) (Tables II-IV). The region-selectivity as well as the dose-dependence of these Mn-induced effects certainly merit further investigation.

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