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Short communication

Effect of prenatal manganese intoxication on [^{3}H]glucose uptake in the brain of rats lesioned as neonates with 6-hydroxydopamine

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Abstract:
In the present study we examined the effects of prenatal manganese (Mn) intoxication on [^{3}H]glucose uptake in the brain of rats lesioned as neonates with 6-hydroxydopamine (6-OHDA). $MnCl_2 \cdot 4H_2O$ (10,000 ppm) was added to the drinking water of pregnant Wistar rats for the duration of pregnancy. On the day of parturition, Mn was discontinued as an additive to the drinking water. The control group consisted of rats that consumed water without Mn. Three days after birth, rats in both groups (control and Mn) were pretreated with desipramine hydrochloride (20 mg/kg) and pargyline hydrochloride (50 mg/kg) and injected bilaterally *icv* with one of three doses of 6-OHDA hydrobromide (15 μg, 30 μg or 67 μg base form in saline on each side) or with saline (control). 6-[^{3}H]-D-glucose (500 μCi/kg, *ip*) was administered to male offspring in adulthood; after 15 min, brain specimens were taken (frontal cortex, hippocampus, striatum, thalamus with hypothalamus, pons and cerebellum) for determination of radioactivity in a liquid scintillation counter. Low dose 6-OHDA (15 μg *icv*) increased [^{3}H]glucose uptake in all brain regions ($p < 0.05$) in both control and Mn-intoxicated animals. In rats lesioned with a moderate dose of 6-OHDA (30 μg *icv*), [^{3}H]glucose uptake was unaltered in both control and Mn-exposed rats. High dose 6-OHDA (67 μg *icv*) reduced [^{3}H]glucose uptake in all brain regions of Mn-exposed rats (except for cerebellum) compared with the saline group (all, $p < 0.05$). There was no change in regional brain uptake of [^{3}H]glucose in control rats. In conclusion, this study shows that mild neuronal insult (15 μg *icv* 6-OHDA) increased glucose uptake in the brain while severe damage (concomitant 60 μg *icv* 6-OHDA and Mn treatment) significantly diminished this process.

Key words:
manganese, 6-hydroxydopamine, CNS, (^{3}H)glucose, rats, prenatal

Abbreviation: CNS – central nervous system, DPM – disintegration per minute, Mn – manganese

Introduction

Manganese (Mn) is a trace element that acts as a co-factor in many enzymatic reactions. In high amounts, however, Mn is overtly neurotoxic, producing motor dysfunction similar to that seen in Parkinson's disease. Studies in rodents and non-human primates have demonstrated that Mn preferentially disrupts the dopaminergic system [9, 31]. The primary source of Mn intoxication in humans is occupational exposure in miners, smelters, welders and workers in dry-cell battery factories; the exposure occurs through inhalation of aerosols or dusts containing high levels of the metal as well as through ingestion [for review see 5]. It is estimated that over 3700 tons of Mn are released into the atmosphere every year, particularly from re-

lease of the gasoline additive methylcyclopentadienyl manganese tricarbonyl.

The effects of Mn on the adult mammalian brain have received considerable attention. On the other hand, the risk of Mn-induced neurotoxicity during brain development, both pre- and postnatally, has received very little attention. Some reports document the neurotoxic effects of Mn on children at various developmental stages following excessive exposure to this metal [44]. It has been suggested that high levels of Mn in drinking water (> 300 μg Mn/liter) are associated with reduced intellectual function in children [43]. Furthermore, Mn toxicity has been described in children receiving long-term parenteral nutrition, manifesting as movement disorders and cholestatic liver disease when parenteral Mn supplementation has been excessive [33]. Mn also could cross the placenta to enter embryos and affect growth of offspring [37], thus, excessive Mn can be an embryotoxicant and fetotoxicant in mammals [11], but the mechanism of this effect has not yet been elucidated. Conversely, the progressive and latent nature of some neurodegenerative disorders (e.g. Alzheimer disease, Parkinson disease, etc.) suggests that the triggering event for these disorders occurs much sooner than the appearance of visible symptoms. Therefore, it is of great importance to identify environmental trigger(s) and to pinpoint the period during which such factors pose the greatest risk and the mechanism(s) involved therein. The abovementioned facts justify the present work in which gestational exposure to Mn was chosen as a model for establishing a link between Mn exposure and increased vulnerability of the central nervous system to the neurotoxic action of 6-hydroxydopamine (6-OHDA).

Heavy metal exposure commonly alters glucose uptake and utilization in brain [3, 10, 46]. Conversely, glucose is the obligate energetic fuel for the central nervous system (CNS) and is the only substrate able to completely sustain neural activity. Its levels represent a net balance among glucose uptake (from the circulation), glucose metabolism to lactate and CO_2, and glucose transport back to the circulation [34]. Among various typical humoral compounds, a number of neuroactive molecules, in particular adenosine, noradrenalin and certain cytokines are involved in glucose metabolism in astrocytes and neurons [1, 2, 21]. Clinical and experimental studies indicate that young developing organisms are more susceptible to xenobiotic- (e.g., heavy metal) induced neurotoxicity, impairing several neurotransmitter systems that participate in cerebral glucose utilization, including the dopaminergic pathway [8, 19, 20, 24–29, 39, 42]. On the other hand, Zwingmann et al. [47] demonstrated that Mn exposure alters brain metabolism. Conversely, from clinical observations, we learn that early stages of Parkinson's disease exhibit progressive changes in regional metabolism at key nodes of the motor and cognitive networks that characterize the illness [18]. Taking the above into consideration, we investigated the effects of prenatal Mn intoxication on [^{3}H]glucose uptake in the brain of rats lesioned with 6-OHDA as neonates.

Materials and Methods

Animals and treatment

Pregnant Wistar rats, 200–220 g, were used in this study. All were housed in a well-ventilated room at 22 ± 2°C with a 12 h light : 12 h dark cycle. From day "1" of pregnancy (i.e., presence of vaginal plugs), rats were singly housed with free access to pelleted food (Altromin-1324, Lage, Germany) and tap water containing 10000 ppm manganese chloride ($MnCl_2 \cdot 4H_2O$) (POCh Ltd., Gliwice, Poland). Fluid consumption by each dam was monitored daily. On the day of parturition, manganese was discontinued, and the litter size was restricted to six pups (preference was given to males).

Three days after birth, rats of both groups (control and manganese exposure) were pretreated with desipramine hydrochloride (20 mg/kg, *ip*, base; 1 h) (Sigma) and pargyline hydrochloride (50 mg/kg, *ip*, salt form; 0.5 h) (Sigma) and injected bilaterally *icv* with 6-OHDA hydrobromide with one of three doses (15 μg, 30 μg or 67 μg base form on each side), or with the vehicle saline (0.85%) – ascorbic acid (0.1%) (control). This procedure has been described in detail [12]. Rats were weaned on the 21st day, at which time, male offspring were group housed until experimentation.

The local Bioethical Committee for Animals, Medical University of Silesia approved the experiment (permission no. 19/06 issued on 01.03.2006). All procedures, reviewed and approved by the Institutional Animal Care Committee, are in accordance with the principles and guidelines described in the NIH booklet *Care and Use of Laboratory Animals*.

Tab. 1. The effect of manganese (10000 ppm) applied during pregnancy on (^{3}H)glucose uptake (DPM/100 mg of wet tissue) in the brain of offspring rats (x ± SEM; n = 5–6)

Part of the brain	Control DPM/100 mg of wet tissue				Prenatally exposured to manganese DPM/100 mg of wet tissue				Two-way analysis of variance:		
	6-OHDA treatment				6-OHDA treatment						
	SALINE	6-OHDA (15 µg *icv*)	6-OHDA (30 µg *icv*)	6-OHDA (67 µg *icv*)	SALINE	6-OHDA (15 µg *icv*)	6-OHDA (30 µg *icv*)	6-OHDA (67 µg *icv*)	groups	substances	both factors
Striatum	27473.3 ± 1126.3	33023.9* ± 1621.5	28480.8 ± 1438.1	25664.4 ± 724.5	31262.4 ± 1124.2	34780.8 ± 2360.8	33435.4 ± 2429.9	23080.8* ± 2585.6	F = 2.42 p < 0.129	F = 12.96 p < 0.001	F = 1.86 p < 0.154
Prefrontal cortex	32637.5 ± 1453.4	39499.0* ± 2166.9	34687.0 ± 1768.4	29555.0 ± 887.5	37393.5 ± 1484.2	42103.5 ± 3163.1	38800.5 ± 3297.0	25136.0* ± 3401.2	F = 1.44 p < 0.23	F = 14.40 p < 0.001	F = 2.05 p < 0.123
Hippocampus	26630.4 ± 1299.1	33456.4* ± 2070.1	28883.3 ± 1538.0	24932.9 ± 808.6	31041.0 ± 1104.3	35307.5 ± 2507.3	34241.5 ± 2656.7	22150.8* ± 2518.0	F = 3.43 p < 0.072	F = 14.65 p < 0.001	F = 2.30 p < 0.093
Thalamus with hypo-thalamus	28617.7 ± 1414.2	37143.5* ± 1997.4	32108.5 ± 1441.8	27012.3 ± 1007.2	33052.5 ± 1209.8	38011.8 ± 2407.4	37916.8 ± 2768.4	24238.8* ± 2925.3	F = 2.84 p < 0.1	F = 17.47 p < 0.001	F = 2.39 p < 0.084
Pons with medulla oblongata	25005.6 ± 1646.2	31223.1* ± 1878.4	26264.0 ± 1192.6	23688.3 ± 920.9	28411.3 ± 936.6	32054.4 ± 2344.9	31367.9 ± 2508.7	20568.3* ± 2199.7	F = 1.93 p < 0.173	F = 12.52 p < 0.001	F = 2.51 p < 0.073
Cerebellum	28760.8 ± 1387.4	36795.7* ± 2184.0	30779.6 ± 1522.7	26966.8 ± 937.7	32398.2 ± 1162.0	37319.3 ± 2679.0	31402.5 ± 8136.2	23442.1 ± 2744.3	F = 0.026 p < 0.874	F = 5.937 p < 0.02	F = 0.569 p < 0.639

Explanation: DPM – disintegration per minute, 6-OHDA – 6-hydroxydopamine *icv*, * $p < 0.05$ as compared with control in the group

In rodents, cumulative doses of up to 5300 mg Mn/kg (during postnatal period) are required to evoke a variable effect on striatal dopamine concentration. Monkey studies showed motor deficits and effects on the globus pallidus at doses > 260 mg Mn/kg. Internal cumulative Mn doses investigated in animal studies are greater than those at which occupationally exposed humans show neurological dysfunction (10–15 mg Mn/kg) [13]. In the present study, we observed that pregnant control rats consumed about 166 ml/kg/24 h tap water, whereas rats treated with manganese chloride solution (10000 ppm) consumed about 125 ml/kg/24 h. The above gave an intake of 348 mg/kg/24 h of Mn^{2+}. After multiplication by 21 days (pregnancy duration), the cumulative dose is calculated to be 7,308 mg/kg. Approximately 10–25% of this metal crosses the placenta [23], so the total dose for each fetus varied between 730–1,820 mg/kg. From veterinary studies, we learned that for mammals (swine) a diet supplemented with 350 ppm to 700 ppm Mn seems to be optimal for this type of study [35].

6-[^{3}H]-D-glucose uptake

Eight weeks after birth, rats were injected *ip* with 6-[^{3}H]-D-glucose (Amersham Radiochemicals, Pittsburgh, PA, USA; 41 Ci/mmol; 0.5 µCi/g BW). After 15 min, the rats were decapitated, their brains were removed and the brains were immediately placed on ice for dissection of the frontal cortex, hippocampus, striatum, thalamus with hypothalamus, pons and cerebellum. Each tissue sample was weighed and placed in a 20 ml scintillation vial containing 1 ml of Soluene-350 (Packard Inc., Downers Grove, Ill., USA). Each vial was then tightly sealed and incubated at 37°C for 48 h, to solubilize tissue. Scintillation cocktail (10 ml, Dimilume-30, Packard Inc., Downers Grove, Ill., USA) was then added, and the vials were briefly vortexed before being counted with a scintillation counter (Liquid Scintillation Counter, DSA 1409, Wallac, Finland). Results are presented as disintegrations per min (DPM) per 100 mg of wet tissue (mean SEM) for each group [26].

Data Analysis

A one- or two-way analysis of variance (ANOVA) and the post-ANOVA test of Neuman-Keuls were used to test the differences between groups for significance. A "p" value of 0.05 or less was used to indicate a significant difference.

Results

There was a trend toward elevated [^{3}H]glucose uptake (DPM) in all brain regions of rats prenatally exposed to Mn versus control rats, by an average of 14% (12.5% in cerebellum to 16.5% in hippocampus). However, differences were of borderline significance (see Tab. 1, two-way analysis of variance; groups).

Low dose 6-OHDA (15 µg *icv*) given on the 3rd day of postnatal life increased [^{3}H]glucose uptake in all brain regions of offspring with no prenatal exposure to Mn. A similar but non-significant elevation was discovered in the brains of rats exposed prenatally to Mn.

In the groups of rats treated with an intermediate dose of 6-OHDA (30 µg *icv*), there was no change in brain [^{3}H]glucose uptake *versus* non-lesioned groups, regardless of prenatal Mn exposure.

High dose 6-OHDA (30 µg *icv*) was associated with a reduction in [^{3}H]glucose uptake only in brains (all regions) of rats exposed prenatally to Mn, *versus* non-lesioned rats.

Discussion

This study demonstrates that the relative extent of 6-OHDA lesioning had qualitatively different effects on [^{3}H]glucose uptake in the brains of rats exposed prenatally to Mn. Low dose 6-OHDA increased brain [^{3}H]glucose uptake in Mn-exposed rats, while a moderate 6-OHDA dose failed to alter brain [^{3}H]glucose uptake in Mn-exposed rats, and high dose 6-OHDA reduced [^{3}H]glucose uptake in Mn-exposed rats (Tab. 1).

These findings contrast with the reduction in glucose uptake and utilization observed after other insults, e.g., ischemia, ethanol and cadmium [15, 40, 41, 45]. Porrino et al. [32] found no differences in the glucose uptake in the brains of MPTP treated monkeys, while chronic L-DOPA (60–120 days) increased cerebral metabolic activity in dopamine-rich regions. Conversely, Mehlhorn et al. [22] demonstrated that a basal forebrain cholinergic lesion resulted in a transient decrease in [^{14}C]D-glucose utilization. They concluded that the cholinergic lesion induced transient upregulation of cortical glucose transporters and that deoxyglucose uptake reflects an increased glucose demand in regions depleted by acetylcholine. Others found that the striatal excitotoxin quinolinic acid profoundly damaged GABAergic neurons and reduced energy metabolism at 1, 5 and 7 weeks post-lesion [4]. If we assume that increased glucose uptake (by neural tissue) more or less reflects neuronal activity, we can hypothesize that the damage produced by either low dose 6-OHDA or Mn is the result of a compensatory increase in glucose uptake and utilization, while high dose 6-OHDA + Mn overwhelms the regenerative ability of neurons and/or glia. It is noteworthy that the 6-OHDA doses, 15, 30 or 67 µg, are associated with a reduction of endogenous striatal dopamine content by 12%, 63% and 85%, respectively, and with a reduction the amount of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) by 21%, 73% and 99%, respectively [12]. Previously, we showed that paraquat (an analog of MPP+, an active metabolite of MPTP) administration produced biphasic reaction on the nigrostriatal system. During the early phase (8 weeks exposure) of paraquat-induced degeneration, surviving dopaminergic nigrostriatal neurons are hyperactive to compensate for the loss of dopaminergic neurons. After 24 weeks exposure, however, these compensatory mechanisms break down, leading to decreased striatal dopaminergic transmission [30]. Clinical data on this subject seem to be rather controversial. Berding et al. [6] demonstrated that global cerebral glucose consumption was reduced in Parkinson's disease patients in comparison to control patients. Others presented the opposite results [17]. It is likely that the type of changes in (an increase or decrease) as well as the intensity of glucose uptake disturbances depends on the severity of nigrostriatal system damage. These results appear to be in agreement with the results of the current study.

Because of a lack of data concerning the molecular mechanism by which Mn affects glucose uptake and metabolism, it is difficult to account for the effect of Mn. As stated previously, glucose levels in the brain are a net balance between uptake, metabolism to lactate and CO_2, and transport back to the circulation. Glucose enters cells *via* the glucose transporters $GLUT_1$ and $GLUT_3$, and several factors are able to modify GLUT protein expression and function [14–16]. Furthermore, glucose metabolism not only meets the energy requirements of the brain, but also provides ribose precursors for the synthesis of nucleosides and NADPH, which is required for the synthesis of lipids

and neurotransmitters as well as for the removal of free radicals [38].

In conclusion, the results of the present study demonstrate that mild neuronal insult (6-OHDA in a dose of 15 μg) increased glucose uptake in the brain while severe damage (concomitant 6-OHDA 60 μg and Mn treatment) significantly diminished this process.

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