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Effects of MnTnHex-2-PyP on Lung Antioxidant Defence System in Asthma Mice Model

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ABSTRACT

We aimed to study the MnTnHex-2-PyP effect on some markers of lung antioxidant defence system in mice asthma model.

The study was carried out on 28 $C_{57}B1/_6$ mice divided into four treatment groups: group 1 – controls; group 2 – injected and inhaled with ovalbumin; group 3 – treated with MnTnHex-2-PyP and inhaled with phosphate buffered saline; group 4 – injected with ovalbumin and MnTnHex-2-PyP but also inhaled with ovalbumin. On days 24, 25 and 26, mice from groups 1 and 2 were inhaled with PBS for 30 min, and those from groups 2 and 4 were given a 1% ovalbumin solution. One hour before inhalation, and 12 hours later the animals from groups 1 and 2 were injected *i.p.* with 100 μl PBS, and those from groups 3 and 4 received a 100 μl MnTnHex-2-PyP solution in PBS, containing 0,05mg/kg. The animals were killed by exsanguination 48 hours after the last inhalation for obtaining a lung homogenate.

The activities of superoxide dismutase, catalase, glutathione peroxidase and the non-protein sulphhydryl group content in the lung homogenate were investigated. Ovalbumin decreased the activities of superoxide dismutase (p=0.01), catalase (p=0.002), glutathione peroxidase and non-protein sulphhydryl groups content (p<0.001) in comparison to controls. In group 4 (ovalbumin and MnTnHex-2-PyP) the activities of superoxide dismutase (p=0.044), catalase (p=0.045), glutathione peroxidase (p=0.002), and the non-protein sulphhydryl groups content (p<0.001) were significantly increased compared to ovalbumin (group 2).

MnTnHex-2-PyP restored the activities of basic enzymes in the lung antioxidant defence system in ovalbumin-induced asthma mice model, 48 hours after the last nebulization.

Keywords: Antioxidants; Asthma; MnTnHex-2-PyP

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INTRODUCTION

Asthma is a serious medical and social problem. This chronic inflammatory disease primarily of the large airways is characterized by eosinophilia, mucus

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hypersecretion and hyperreactivity to inhaled allergens, causing increased vascular permeability.[1,2] An essential element in the disease is the imbalance between Th_1 and Th_2 cells at the expense of predominant Th_2 phenotype.[3,4] The Th_2 response to allergic inflammation through the secretion of IL_4, IL_5 and IL_{13}, leads to accumulation and activation of eosinophils, activation of fat cells and an increase in the IgE level.[4] Inflammatory cells, accumulated in asthmatic airways have the exceptional capacity to produce reactive oxygen species (ROS). ROS play a critical role in the pathogenesis of airway inflammation.[5,6] ROS induce dysfunction of the endothelial barrier with subsequent increased permeability of fluid, macromolecules, and inflammatory cells.[7] In normal lungs, the balance between oxidants and antioxidants is enough to keep lining fluid in the airways and extracellular spaces in the highly reduced state and maintain the normal physiological functions. The increase in oxidants and/or the decrease of antioxidants can destroy this balance causing an oxidative stress which may be associated with various lung diseases including asthma.[5] Recent evidence suggests that antioxidants are capable of reducing inflammation and airway hyperreactivity in asthma.[8,9] Demand for new, powerful antioxidants to treat a wide range of diseases, resulting from increased lipid peroxidation, has been particularly relevant in recent years. Thus synthetic antioxidants such as metal complexes (Mn salens, Mn cyclic polyamines, Mn porphyrins and nitroxides) have been developed. Given the key role of mitochondria, compounds, such as Mn porphyrins that accumulate there, are of particular interest.[10] Therefore, we aimed to study the effects of one mangan *meso* porphyrin, MnTnHex-2-PyP, on some markers of lung antioxidant defence system in allergic mice model.

MATERIAL AND METHODS

Chemicals

Ovalbimin, grade V and Phosphate buffered saline (PBS) were purchased from Sigma-Aldrich Company and Imject Alum® was purchased from Pierce Chemical Company (USA).

MnTnHex-2-PyP (Manganese (III) 5,10,15,20-tetrakis(N-hexylpyridinium-2-yl) porphyrin) was kindly provided by Ines Batinić-Haberle from the Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina, USA.

Animals and Experimental Protocol

The experiment was performed in accordance with the Animal Welfare Regulations and was approved by the University Ethics Committee.

The study was carried out on 24 female C57Bl/6 mice (weight 20±2.0g, 8-10 weeks old). The animals were raised at the University vivarium at a temperature of 22±2°C and humidity of 50±10%, given normal pelleted diet and water *ad libidum*. The mice were divided into four groups: group 1, controls; group 2, injected with ovalbumin (OVA); group 3, treated with MnTnHex-2-PyP, and group 4, treated with OVA and MnTnHex-2-PyP. The animals from groups 1 and 3 were injected *i.p.* with a 100 µL phosphate-buffed saline (PBS) + Imject Alum (1:1) on days 0 and 14. The animals from groups 2 and 4 were injected with a 100 µL ovalbumin solution, containing 20 µg OVA (p0012-protocol) on the same days. On days 24, 25 and 26, mice from groups 1 and 2 were given inhalation with PBS for 30 min, and those from groups 2 and 4 were given inhalation with a 1% ovalbumin solution (OVA dissolved in PBS). For this purpose, a special plexiglass chamber was used. One hour before inhalation and 12 hour later, the animals from groups 1 and 2 were injected *i.p.* with 100 µL PBS, and those from groups 3 and 4 received a 100 µL MnTnHex-2-PyP solution in PBS, containing 0.05mg/kg. The solution was sterilized by filtration through 0.2 µm filters. For all injections, individual sterile needles were used.

Biochemical Assays in the Lung Homogenate

The animals were sacrificed on day 28 (48 hours after the last inhalation) under thiopental anesthesia (50mg/kg). The chest was opened and the lungs were perfused *in situ* via the right heart ventricle with saline (10 mL). The right lung was ligated at the hilus, cut and then removed from the chest and used to prepare the lung homogenate. The tissue was homogenized with ice-cold 0.25 M sucrose in Tris HCl, pH 7.4, in 1:10 ratio. The homogenate was centrifuged (9000 x g, 30 min), and the supernatant was stored on ice. The superoxide dismutase (SOD) activity in U/mg lung tissue was determined by the method of Maral et al.,[11] and catalase (CAT) activity in mcat/g tissue was assessed by the method of Koroljuk et al.[12] The activity of glutathione peroxidase (GP) in U/g lung tissue was measured by the method of Bernchnaider, modified by Pereslegina.[13] The non-protein sulphhydryl (NPSH)

groups content in mol x 10^{-7}/g tissue was measured by the method of DeLucia et al.[14]

Statistical Analysis

The experimental data were analyzed using Statgraphics plus for Windows 5.0. Statistical analysis was based on parametric methods. Student's t-test was used to compare the means of samples. $P<0.05$ were considered statistically significant.

RESULTS

The activities of superoxide dismutase and catalase in group 2 (asthma-induced) decreased significantly in the lung homogenate, 71% ($p=0.01$) and 74% ($p=0.002$), respectively, as compared with the control animals. The decrease in group 4 was lower, 96.6%, ($p=0.044$, comparable to OVA group) and 97% ($p=0.045$), statistically significant as compared to group 2, respectively (Table 1, Figure 1, Figure 2). Changes in the glutathione peroxidase activity showed a similar dynamics, such as a decrease in the OVA group (71%) and in the values approximate to those of the controls in group 4 ($p=0.002$ in comparison to group 2), (Table 1, Figure 3). The non-protein sulphhydryl (NPSH) group content in the lung homogenate decreased to 68% in group 2 ($p<0.001$), and in the group with OVA and antioxidant (group 4) this decrease was relatively lower (93%), ($p<0.001$) as compared to the OVA group (Table 1, Figure 4).

Table 1. Effect of MnTnHex-2-PyP on the activity of some enzymes of lung antioxidant defence system in mice model of asthma

Parameters \ Groups	28 day after treatment (48 hours after the last inhalation)			
	Control	OVA	MnTnHex-2-PyP	OVA+MnTnHex-2-PyP
SOD activity in U/g	31.1±1.78	22.1±2.37*	30.8±1.83	30.0±2.05†
CAT activity in mcat/g	38.3±1.90	28.5±1.78*	36.84±2.57	37.2±2.50†
GP activity in U/g	105.7±14.6	75.7±2.7	105.7±11.8	116.40±8.4†
NPSH groups mol/g x 10^{-7}	0.58±0.022	0.40±0.032*	0.51±0.052	0.53±0.017†

Abbreviations: OVA, ovalbumin; MnTnHex-2-PyP, Manganese (III) 5,10,15,20-tetrakis(N-hexylpyridinium-2-yl) porphyrin; SOD, superoxide dismutase; CAT, catalase; GP, glutathion peroxidase; NPSH groups, non protein sulphhydryl groups. Data were presented as mean±SEM.

*- Different from control at $p<0.05$ b by analysis of variance

†- Different from group 2 (OVA) at $p<0.05$ by analysis of variance

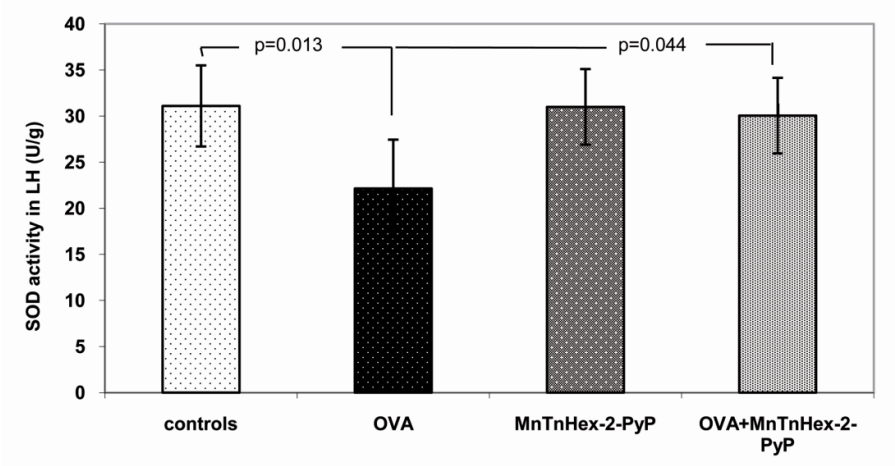

Figure 1. Superoxide dismutase (SOD) activity in lung homogenate. Each point represents the mean±SD for six mice.

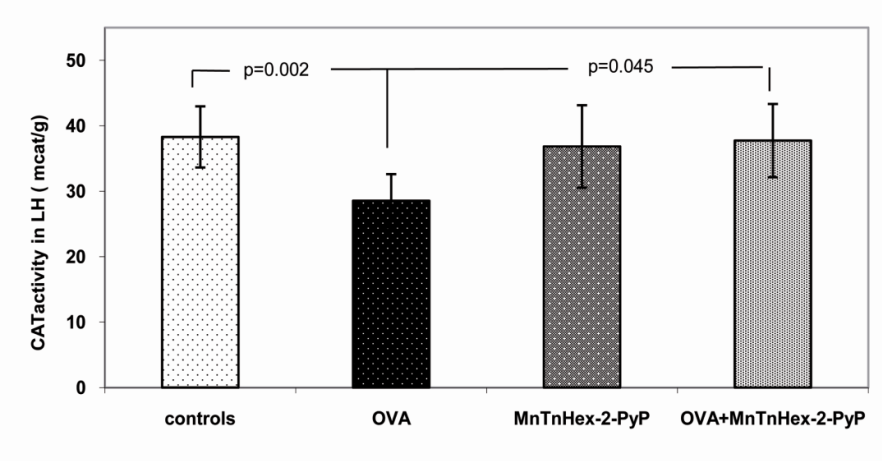

Figure 2. Catalase (CAT) activity in lung homogenate. Each point represents the mean±SD for six mice.

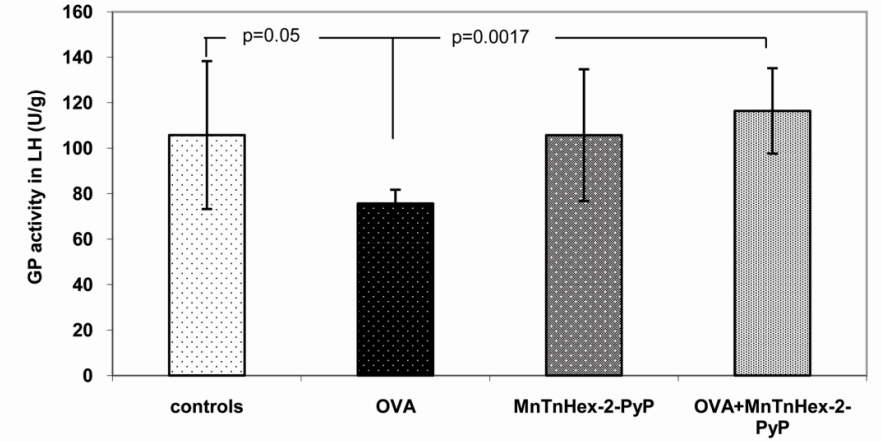

Figure 3. Glutathione peroxidase (GP) activity in lung homogenate. Each point represents the mean±SD for six mice.

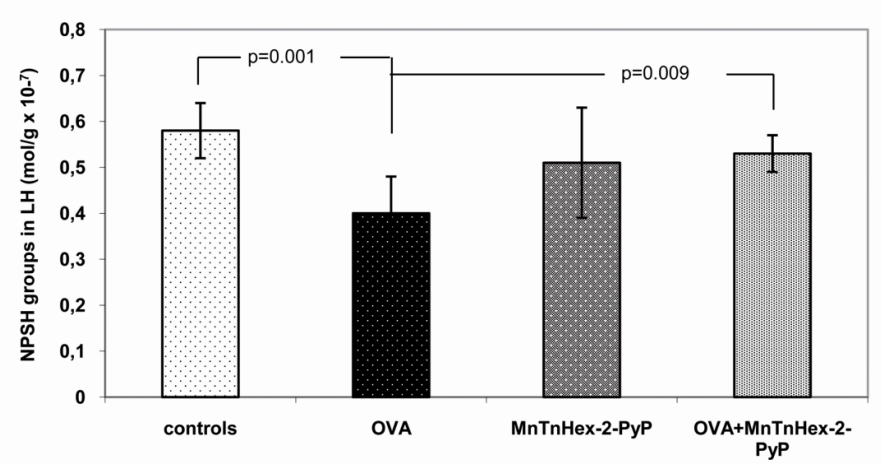

Figure 4. Non protein sulphhydryl groups (NPSH) content in lung homogenate. Each point represents the mean±SD for six mice.

DISCUSSION

The results we obtained clearly showed that the sensitization and inhalation with ovalbumin induced an oxidative stress in mice, which play a critical role in the development of allergic asthma (decreased activity of antioxidant enzymes-SOD, CAT, GP and NPSH groups). These results support the idea that asthma is a disease associated with oxidative stress.[5] In conditions of oxidative stress, an imbalance between oxidants and antioxidant is often seen and some of the main antioxidants are depleted. Results similar to ours are cited in the literature. The increased activities of the enzymes GP and SOD in lung cells, and the products of lipid peroxidation in lung, sputum and urine were proven.[15,16] Fair reduction of the indicators of lipid peroxidation and significantly less reduction in the activity of key antioxidant enzymes induced by antioxidants, give us reason to believe that manganese *meso*-porphyrins have a beneficial effect on an ovalbumin-induced asthma. Mn(III) *N*-alkylpyridylporphyrins are among the most potent known SOD mimics and catalytic peroxynitrite scavengers and modulators of redox-based cellular transcriptional activity. In addition to their intrinsic antioxidant capacity, bioavailability plays a major role in their *in vivo* efficacy.[17] They have at least four antioxidant properties, such as the removal of superoxide ($O2^{-}$), hydrogen peroxide (H_2O_2), peroxinitrite ($ONOO^{-}$) and lipid peroxides.[18,19] We used one of the catalytic manganese metaloporphyrins, MnTnHex-2-PyP, a hexyl analogue of the lead compound MnTE-2-PyP. It was considerably more lipophilic than MnTE-2-PyP,[20] and about 30-fold more effective in protecting aerobic growth of SOD-deficient *E.coli*.[21] In animal models, the lipophilic MnTnHex-2-PyP is up to 120 times more efficient in reducing oxidative stress injuries than hydrophilic MnTE-2-PyP, at lowest therapeutically relevant doses (0.05 mg/kg).[20,22,23] We introduced the antioxidant twice, because the plasma half-life in *i.p.* introduction of 10 mg/kg MnTE-2-PyP in mice is about 1 hour. It accumulates in all organs: liver, kidney, spleen, heart, lungs and brain, and the half-life in the body is significantly longer ranging from 60-135 hours.[24,25] No data on the toxicokinetics of MnTnHex-2-PyP are available. A decrease in the markers of lipid peroxidation and the recovery of the activities of basic enzymes of the antioxidant defence system in allergic asthma mice model were explained by the properties of *meso-manganese* porphyrins. Saba et al. show that $MnTnHex\text{-}2\text{-}PyP^{5+}$ is active in the amelioration of renal and mitochondrial damage in ischemia/reperfusion injury in a single dose, less than 50μg/kg, one of the lowest, if not the lowest among the antioxidants used in animal models of oxidative stress.[23] Therefore, we used the antioxidant in a daily dose of 0.1 mg/kg, divided into two doses at 0.05 mg/kg. The distribution of MnTnHex-2-PyP in the liver cells showed that it is localized mainly in mitochondria (~90%). Mitochondrial location is roughly proportional to the number of carbon atoms in the N-alkilpiridyl chains and is also proportional to the lipophilicity of mangan porphyrins. This explains the significant biological resolution of MnTnHex-2-PyP to suppress oxidative stress induced damage in different animal models (Spasojevic I et al. unpublished data). The exact mechanism of metalloporphyrin-mediated inhibition of lipid peroxidation is not known, but it is thought to be similar to the mode of action described for metalloporphyrin-scavenging of $ONOO^{-}$. Metalloporphyrins catalyze numerous redox reactions.[26] Manganese porphyrins, in particular, have been used as redox catalysts in several model systems relevant to biochemistry, for instance, superoxide dismutase and catalase mimics.[20,27] Manganese porphyrins with the highest superoxide dismutase activities (MnOBTM-4-PyP and MnTM-2-Pyp) were the most potent inhibitors of lipid peroxidation with calculated IC50s of 1.3 and 1.0 μM, respectively. These manganese porphyrins were two orders of magnitude more potent than either Throlox (IC50+204 μM) or Rutin (IC50+112 μM).[28] The most potent porphyrin-based compounds developed on the basis of structure-activity relationships, such as Mn(III) *meso*-tetrakis(N-ethylpyridinium-2-yl)porphyrin (MnTE-2-PyP), its hexyl analogue (MnTnHex-2-PyP), and Mn(III) *meso*-tetrakis(N,N'-diethylimidazolium-2-yl)porphyrin bear positively charged *ortho* pyridyl or di-*ortho* imidazolyl moeties close to the metal site.[29] Another critical parameter for the *in vivo* efficacy of Mn porphyrins is their bioavailability.[21,23] MnTnHex-2-PyP differs from MnTBAP in that it is rapidly reduced *in vivo* by numerous flavoenzymes.[30,31] This quick reduction plays a major role in the antioxidant activity of this and other Mn (III) *ortho*-N-alkylporphyrin.[31] The effects, observed after Mn porphyrins use were the consequence not only of mere scavenging of ROS/RNS

(reactive nitrogen species), but also of Mn porphyrins being able to modulate ROS/RNS-based signaling pathways. MnTE-2-PyP, a potent SOD mimic/$ONOO^-$ scavenger, can strongly inhibit excessive activation of redox-sensitive cellular transcriptional activity, particularly suppressing hypoxia inducible factor 1α (HIF-1α) activation.[32] This results in lowering the number of inflammatory cells and cytokines, which in turn could lower to the levels of secondary ROS/RNS.[33] Manganese *meso* porphyrins have been used successfully to treat oxidative stress in the murine model of OVA-induced asthma.[34,35] MnTE-2-PyP, MnTnHex-2-PyP and MnTDE-2-ImP show significant protection in the lungs of mammals after irradiation.[22,32,36,37]

Ovalbumin-sensitized and -inhaled mice developed an allergic asthma characterized by an oxidative stress. MnTnHex-2-PyP, administered *i.p.* twice in a single dose of 0.05mg/kg every 12 hours during inhalation with ovalbumin restored the activity of the antioxidant enzymes in the lung, 48 hours after the last inhalation.

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