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SYNTHETIC METALLOPORPHYRINS A CLASS OF PHARMACOLOGICAL INTEREST

***Pradeep V.Khandelwal, #Avijit Mazumder,**
$Sujit Chaudhari

** Ph D Research Scholar*
#Department of Pharmacy, Noida Institute of Engineering and Technology, Greater Noida

ABSTRACT

This paper presents a review summary of the Pharmacological effects of Metalloporphyrins in Hypobaric hypoxia stress condition. The hypobaric hypoxia conditions leads to significant oxidative stress in humans. We proposed to study the effects of hypobaric hypoxia on hemeoxygenase level and also to correlate the role of Metalloporphyrins in modulating hemeoxygenase expression and the physiologic significance of hemeoxygenase induction and suppression in oxidative stress induced by hypobaric hypoxia. The Metalloporphyrins are a class of drug known for modulating the hemeoxygenase activity. Different Metalloporphyrins may cause various response at different levels of cellular activity.

Keywords:- *Metalloporphyrins; Pharmacology; Biochemistry; Superoxide; Antioxidant; Oxidative Species*

INTRODUCTION

Porphyrins which are combined with a Metal ion. The metal is bound equally to all four nitrogen atoms of the pyrrole rings. They possess characteristic absorption spectra which can be utilized for identification or quantitative estimation of porphyrins and porphyrin-bound compounds. Metalloporphyrins is a therapeutic catalytic anti-oxidant.

Metalloporphyrins have a novel class of catalytic antioxidants that scavenge a wide range of reactive oxygen species such as superoxide, peroxide, peroxynitrite and lipid peroxyl radicals.

The structure of Metalloporphyrins contains a type of metal centre, redox potential and electrostatic charge of the compounds. These are recognized as important determinants of their antioxidant activity and potency. These concepts have beneficial for the development of Metalloporphyrins with specific activities. Several compounds in this class have been shown to be efficacious in a variety of *in vitro* and *in vivo* oxidative stress models of human diseases.

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MATERIALS AND METHODS

Drug Used:-

Synthetic Metalloporphyrins (Cobalt (III)Protoporphyrins (CoPPIX),Fe (III) Protoporphyrins (FePPIX). Metalloporphyrins are photosensitive therefore stored in ambered colour dark container and all solution prepared in subdued light.

They were dissolved in 0.2 M Sodium hydroxide solution, adjusted ph 7.4and diluted with 0.85 % Sodium Chloride solution.

Experimental Animals:-

Adult Male Rats of Wister Strain weighing 250±20 gm were used in the study. The experiments were performed after approval by the Institutional Ethical's Committee for research on Animals. The rats were selected at random from the stock colony.

Planning of Experiments:-

Animal were divided into ten groups of six rats each. Drugs were given intraperitoneally for five days. Animals were exposed to hypobaric hypoxia on the fifth day after dosing.

Experimental Conditions:-

The room was maintained at 25ºC ±2 ºC, % RH 40 to 60 % and 12 hours light per dark cycle. Animals were anesthetized using Ketamine 50mg/kg in combination with Xylazine 5 mg/kg.

OPERATIVE PROCEDURE

After five days of Metalloporphyrins treatment as per the schedule, animals were exposed to hypoxia for three hours and were sacrificed by cervical dislocation immediately after removal from hypoxia chamber for biological experiments. Equal number Metalloporphyrins treated groups (group III, group V, group VII, group IX) were also sacrificed. Brain ,heart ,lung and liver were quickly removed in Ice-cold saline, perfused, cleaned ,wiped, dried and weighed and were processed for the estimation of enzyme assays and other biochemical parameters.

STATISTICAL EVALUATION OF RESULTS

The data obtained in the present study have been subjected statistical evaluation using the statistical software Graph pad Prism (version 4). Statistical analysis was done using analysis of Variance (ANOVA) and Tukey Krammer test for multiple comparisons. P values less than 0.05were considered significant.

Eqn 1. Hydroxyl radical formation

$$Fe^{3+} + O_2^- \longrightarrow Fe^{2+} + O_2$$

(O_2^- reducing the iron salt)

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$$

(Fenton reaction)

$$O_2^- + H_2O_2 \longrightarrow O_2 + {}^{\bullet}OH + OH^-$$

(metal catalyzed Haber–Weiss reaction)

Eqn 2. Peroxynitrite formation

$$NO + O_2^- \longrightarrow ONOO^-$$

Eqn 3. Superoxide dismutation reaction

$$O_2^- \longrightarrow O_2 + e^-$$

$$O_2^- + e^- + 2H^+ \longrightarrow H_2O_2$$

$$2O_2^- + 2H^+ \longrightarrow O_2 + H_2O_2$$

Eqn 4. Hydrogen peroxide dismutation reaction

$$H_2O_2 \longrightarrow O_2 + 2e^- + 2H^+$$

$$H_2O_2 + 2e^- + 2H^+ \longrightarrow 2H_2O$$

$$2H_2O_2 \longrightarrow O_2 + 2H_2O$$

Reaction 1: Chemical reactions by which some reactive oxygen species are formed

RESULTS

The Metalloporphyrins treatments on expression at mRNA and protein level and on hemeoxygenase activity in hypoxia and normoxic condition, on Lipid peroxidation, on Catalase, on GPx, on GSH ,on Glutathione reductase, on GST in hypoxia and normoxic condition.

DISCUSSION

Hypoxia leads to serious cardiovascular morbidity, pulmonary hypertension ventricular hypertrophy, cardiac arrhythmia and myocardial infarction myocarditis etc. Heart rate (HR) is controlled by the balance between parasympathetic (PNS) and sympathetic nervous system (SNS) activities imposed on the spontaneous discharge frequency of the sinoatrial node. On a beat to beat basis, HR is not constant. Rather, there are fluctuations that are indicative of the relative contributions of each of these components of the autonomic nervous system.(Saul, J.P. 1990).
Altitude exposure is known to modulate the parasympathetic and sympathetic neural balance to the heart (Richarlet et.al., 1990; Wolfel et al., 1991). Yet there have been few studies of HR control at altitude. Ventricular chamber stiffness increased substantially during altitude hypoxia.

SUMMARY

The aim of the present study was to investigate the effect of hypobaric hypoxia on the cardiovascular system in conscious animals and it's modulation by hemeoxygenase. For this hemeoxygenase levels (mRNA, Protein and enzyme activity) in brain, heart, lung and liver were compared in normoxic and hypobaric hypoxic conditions under simulation in a hypoxic chamber (20,000 feet for 3 hour) in the presence of hemeoxygenase modulators viz HO-1 inducers (CoPPIX, FePPIX) and HO-1 inhibitors (SnPPIX and ZnPPIX). We further analyzed if the hypoxic stress was reflected in measurement of oxidative stress m arkers (malonaldehyde) in these organs and the status of first line antioxidants viz catalase and glutathione peroxidase. The effect of Phase II metabolizing enzymes was also studied in all the groups. Since pharmacological modulators (Metalloporphyrins) were used in an attempt to modulate hemeoxygenase, tissue damage markers, and histopathological changes in target organs were also studied. Also the physiological impact of this modulation by Metalloporphyrins was compared on functioning of the heart in conscious rats.

REFERENCES

[1] Abraham NG, Drummond GS, Lutton, JD, Kappas A. The biological Significance and physiological role of heme oxygenase, Cell. Physiol Biochem. 1996; 6:129-168.

[2] Abraham NG. Therapeutic Applications of Human Heme Oxygenase Gene Transfer and Gene Therapy. Curr Pharm design. 2003; 9(30): 2513- 2524.

[3] Aithal PG, Day CP. The natural history of histological proved drug induced Liver disease.Gut.1999; 44(5);731-5

[4] Bailey D, Davies B, Davison G, and Young I, Oxidatively stressed out at High altitude. Int Soc Mount Med Newsl, 2000; 10: 3-13.

[5] Bailey, D.M., Davies, B., Young, I.S., Intermittent hypoxic training Implications of lipid peroxidation induced by acute normoxic exercise in active men. Clin Sci (Lond), 2001; 101: 465-475

[6] Cadenas E. Biochemistry of oxygen toxicity. Annual Review of Biochemistry, 1989; 58: 79- 110

[7] Danielson UH, and Manneriveik KB, Kinetic independence of the subunits of cytosolic glutathione transferase from the rat, Biochem J, 1985; 231: 263-7.

[8] Eisenstein RS, Gracia-Mayol D, Pettingell W, Munroe HN. Regulation of ferritin and hemeoxygenase in rat fibroblasts by different forms of iron. Proc. Natl. Acad Sci. USA. 1991; 88: 688-692.

[9] Ficicilar H., Zergeroglu A.M., Tekin D., and Ersoz G. The effects of Exercise on plasma antioxidant status and platelet response Thrombus. Res.2003; 111; 267-271

[10] Graminski GF, Kubo Y, Armstrong RN. Spectroscopic and kinetic evidence for the thiolate anion of glutathione at the active site of glutathione S-transferase. Biochemistry. 1989 Apr 18; 28(8):3562-8.

[11] Kehrer JP. The Haber-Wiess Reaction and Mechanisms of Toxicity. Toxicology 2000, 149, 43-50.

[12] LaManna JC, Chavez JC, Pichiule P. Structural and functional adaptation To hypoxia in rat brain. J Exp Biol 2004; 207:3163-9

[13] Magalhaes J, Ascensao A, Viscor G, Soares J, Oliviera J Marques F, Duar te J. (2004a) Oxidative stress in hum ans during and after 4 hours of Hypoxia at simulated altitude of 5500m Aviat space Environ Med 2004; 75:16-22.

[14] Nayer WG, Grau A, Slade A. A protective effect of verapam il on hypoxic heart muscle.Cardiovasc Res.1976; 10(6): 650-62

[15] Oberle S, Schwartz P, Abate A, Schroder H. The antioxidant defense protein ferritin is a novel and specific target for penta erithrityl tetranitrate in endothelial cells. Biochem Biophys. Res. Commun. 1999; 261: 28-34.

[16] Paglia DE, Valentine WN. Studies on the quantitative and qualitative Characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 1967, 70: 1-58.

[17] Quinlan GJ, Chen Y, Evans, TW, Gutteridge, JM. Iron signaling Regulated directly and through oxygen: Implication for sepsis and the acute respiratory distress syndrome Clin. Sci. (Colch.).2001; 100:169-182.