UNIVERSITI SAINS MALAYSIA
GERAN PENYELIDIKAN UNIVERSITI
PENYELIDIKAN
LAPORAN AKHIR

STUDIES ON NITRIC OXIDE (NO), CITRULLINE-NO CYCLE ENZMES, ARGINASE, GLUTAMINE SYNTHETASE AND OXIDATIVE STATUS IN ANOXIA (HYPOBARIC HYPOXIA) AND REPERFUSION STATES IN RAT BRAIN

PENYELIDIK

DR. MUMMEDY SWAMY

PENYELIDIK BERSAMA

DR. K.N.S. SIRAJUDEEN
CHANDRAN GOVINDASAMY

2012

FINAL REPORT
FUNDAMENTAL RESEARCH GRANT SCHEME (FRGS)
Laporan Akhir Skim Geran Penyelidikan Asas (FRGS) IPT
Pindaan 1/2009

A

RESEARCH TITLE : **Studies on Nitric oxide (NO), Citrulline-NO cycle enzmes, arginase, glutamine synthetase and Oxidative status in anoxia (Hypobaric hypoxia) and reperfusion states in rat brain**
Tajuk Penyelidikan

PROJECT LEADER : **DR. MUMMEDY SWAMY**
Ketua Projek

PROJECT MEMBERS (including GRA) : 1. **Dr. K. N. S. Sirajudeen**
2. **En. Chandran Govindasamy**
Ahli Projek

PROJECT ACHIEVEMENT *(Prestasi Projek)*

B

ACHIEVEMENT PERCENTAGE			
Project progress according to milestones achieved up to this period	**0 - 50%**	**51 - 75%**	**76 - 100%**
Percentage			100%

RESEARCH FINDINGS		
Number of articles/ manuscripts/ books	**Indexed Journal**	***Non-Indexed Journal***
	1 (Under review, Manuscript enclosed)	Nil
Paper presentations	**International**	***National***
	1	1
Others (Please specify)	Dessertation of Dr. Mohd Jamsani bin Mat Saleh for M. Path. Chemical Pathology – under preparation.	

HUMAN CAPITAL DEVELOPMENT

Human Capital	Number		Others (Please specify):
	On-going	Graduated	
PhD Student			M.Path ongoing 1 student **(Dr. Mohd Jamsani bin Mat Saleh)**
Masters Student			
Undergraduate Students			
Temporary Research Officer			
Temporary Research Assistant			
Total	1		

EXPENDITURE *Perbelanjaan*

C

Budget Approved *(Peruntukan diluluskan)* : **RM 39000.00**
Amount Spent *(Jumlah Perbelanjaan)* : **RM 36958.80**

Balance *(Baki)* : **RM 2041.20**
Percentage of Amount Spent : 94.77 %
(Peratusan Belanja)

ADDITIONAL RESEARCH ACTIVITIES THAT CONTRIBUTE TOWARDS DEVELOPING SOFT AND HARD SKILLS *(Nyatakan Penyelidikan Tambahan yang menyumbang kepada pembangunan kemahiran insaniah)*

D

International

Activity	Date (Month, Year)	Organizer
Invited lecture at International conference on Advances in free radical research, natural products, anti oxidents and radioprotectors in health & 9th Annual Meeting of the Society of Free Radical Research – India. Hotel Marriott courtyard, Hyderabad India.	11th – 13th January 2010	NIMS, University of Hyderabad, SFRR India, Ohio Stat Med Centere USA.

National

Activity	Date (Month, Year)	Organizer
8th annual Scientific and general Meeting, College of Pathologists, Academy of Medicine, Renaissance Kota Bharu Hotel, Kelantan, Malaysia,	6th – 7th June 2009	The collge of Pathologists Academy of Medicine, Malaysia

PROBLEMS / CONSTRAINTS IF ANY *(Masalah / Kekangan sekiranya ada)*

E Nil

RECOMMENDATION *(Cadangan Penambahbaikan)*

F

RESEARCH ABSTRACT – Not More Than 200 Words *(Abstrak Penyelidikan – Tidak Melebihi 200 patah perkataan)*

G Nitric oxide is postulated to be involved in the pathophysiology of neurological disorders due to hypoxia/ anoxia in brain due to increased release of glutamate and activation of N-methyl-D-aspartate receptors. Reactive oxygen species have been implicated in pathophysiology of many neurological disorders and in brain function. To understand their role in anoxia (hypobaric hypoxia) and reperfusion (reoxygenation), the nitric oxide synthase, argininosuccinate synthetase, argininosuccinate lyase, glutamine synthetase and arginase activities along with the concentration of nitrate /nitrite, thiobarbituric acid reactive substances and total antioxidant status were estimated in cerebral cortex, cerebellum and brain stem of rats subjected to anoxia and reperfusion. The results of this study clearly demonstrated the increased production of nitric oxide by increased activity of nitric oxide synthase. The increased activities of argininosuccinate synthetase and argininosuccinate lyase suggest the increased and effective recycling of citrulline to arginine in anoxia, making nitric oxide production more effective and contributing to its toxic effects. The decreased activity of glutamine synthetase may favor the prolonged availability of glutamic acid causing excitotoxicity leading to neuronal damage in anoxia and reperfusion. The increased formation of thiobarbituric acid reactive substances and decreased total antioxidant status indicate the presence of oxidative stress in anoxia and reperfusion. The increased arginase and sustained decrease of GS activity in reperfusion group likely to be protective.

Date : 16/03/2010
Tarikh

COMMENTS, IF ANY / ENDORSEMENT BY RESEARCH MANAGEMENT CENTER (RMC)
(Komen, sekiranya ada / Pengesahan oleh Pusat Pengurusan Penyelidikan)

H .....

.....

.....

Name:
Nama:

Signature:
Tandatangan:

Date:
Tarikh:

UNIVERSITI SAINS MALAYSIA
JABATAN BENDAHARI
KUMPULAN WANG PENYELIDIKAN FUNDAMENTAL
PENYATA PERBELANJAAN SEHINGGA 28 FEBRUARI 2010

Jumlah Geran	RM39, 000.00	Ketua Projek	DR MUMMEDY SWAMY
Peruntukan 2007 (Tahun 1)	RM25,000.00	Tajuk Projek	STUDIES ON NITRIC OXIDE (NO), CITRULLINE-NO-CYCLE ENZYMES, ARGINASE, GLUTAMINE SYNTHETASE AND OXIDATIVE STATUS IN ANOXIA (HYPOBARIC HYPOXIA) AND REPERFUSION STATES IN RAT BRAIN
Peruntukan 2008 (Tahun 2)	RM9,000.00	Tempoh	36 BULAN (JAN 2007- JAN 2010)
Peruntukan 2009 (Tahun 3)	RM5,000.00	No. Akaun	203/PPSP/6170027

Kwgan	Akaun	PTJ	Projek	Peruntukan Projek	Perbelanjaan Terkumpul sehingga Tahun lalu	Peruntukan Semasa	Tanggungan Semasa	Bayaran Tahun Semasa	Belanja Tahun Semasa	Baki Projek
203	11000	PPSP	6170027		-	-	-	-	-	-
203	14000	PPSP	6170027	-	-	-	-	-	-	-
203	15000	PPSP	6170027	-	-	-	-	-	-	-
203	21000	PPSP	6170027	5,000.00	2,805.00	2,195.00	-	1,847.80	1,847.80	347.20
203	22000	PPSP	6170027	-	-	-	-	-	-	-
203	23000	PPSP	6170027	1,500.00	-	1,500.00	-	-	-	1,500.00
203	25000	PPSP	6170027	-	-	-	-	-	-	-
203	26000	PPSP	6170027	-	-	-	-	-	-	-
203	27000	PPSP	6170027	28,500.00	31,186.00	(2,686.00)			-	(2,686.00)
203	28000	PPSP	6170027	-	-	-	-	-	-	-
203	29000	PPSP	6170027	4,000.00	1,120.00	2,880.00	-		-	2,880.00
203	35000	PPSP	6170027	-	-	-	-	-	-	-
				39,000.00	35,111.00	3,889.00	-	1,847.80	1,847.80	2,041.20

International Conference on Advances in Free Radicals Research, Natural Products, Antioxidants and Radioprotectors in Health & Ninth Annual Meeting of the Society of Free Radical Research India

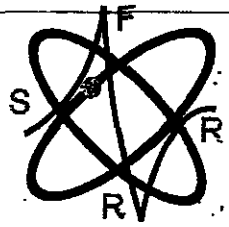
January 11th-13th, 2010

Abstracts

Venue:
Convention Centre, Hotel Marriott Courtyard, Hyderabad

Organised By:
Nizam's Institute of Medical Sciences, Hyderabad,
University of Hyderabad, Hyderabad &
Davis Heart & Lung Research Institute, Ohio State University, Columbus, USA

OHIO STATE Medical Center



Proceedings of International Conference on Advances in Free Radicals Research, Natural Products, Antioxidants and Radioprotectors in Health & Ninth Annual Meeting of the Society of Free Radical Research-India

January 11th - 13th, 2010

Edited by:
Prof. P Reddanna
Dr. K Vijay Kumar

Organised by:

Nizam's Institute of Medical Sciences, Hyderabad,
University of Hyderabad, Hyderabad &
Davis Heart & Lung Research Institute, Ohio State University, Columbus, USA

IL71. Modulation by Nitric Oxide (NO) of Neurobehavioral and Immunological Responses During Stress

Arunabha Ray, Ayanabha Chakraborty and Kavita Gulati

Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007. Email: arunabha14@yahoo.co.in , 9818037595

Stress is defined as any aversive stimuli capable of disrupting the physiological milieu and the ability to cope with such stressful situations is a critical factor in disease prevention or amelioration. Adaptogens are agents which protect or reverse stress effects on the biological system, and though several such agents are available in both traditional and modern systems of medicine, a clearcut evidence based strategy for stress management with drugs is still not available. Today, stress is recognized as a highly interactive phenomenon in which the CNS, the neuroendocrine and immune systems are key players in tandem. Nitric oxide (NO) is a ubiquitous, multidimensional molecule, which has a wide array of regulatory functions in the biological system. In view of the extensive distribution of NO in several body systems, some of which are responsive to stress, the possible role of NO during stress and stress mediated reactions were investigated. Using restraint stress (RS) as the conventional experimental model in rodents, we evaluated the basis of NO involvement in stress induced biological changes. RS induced (a) neurobehavioral suppression in the elevated plus maze test, (b) elevated plasma corticosterone, and (c) lowering of brain NO metabolite (NOx) levels. Pretreatment with the NO mimetics, L-arginine and isosorbide dinitrate (ISDN) attenuated these effects, whereas, the NO synthase inhibitors, L-NAME and 7-nitroindazole aggravated them. In experiments with chronic stress, repeated RS exposure resulted in neurobehavioral tolerance, and effects that was accompanied by elevated NOx levels in the brain, suggestive of reversal of acute stress effects after chronic RS. Levels of the endogenous NOS inhibitor, ADMA, were elevated in the RS situation, as compared to the no RS situation. Male rats were more susceptible to RS effects as compared to female rats, and these differences could be attributed to differential NOx and ADMA levels in the brain tissue. Experiments showed that the emotionality rating of rats could also be defined on the basis of NO. In addition, the anti-stress effects of some centrally acting drugs like diazepam and morphine were also linked to changing levels of NOx in the brain and plasma. Further, in immunized rats, RS suppressed markers of both humoral and cell mediated immunity, and influenced the cytokine profile. Pretreatment with NO mimetics attenuated these stress responses by differing degrees, whereas, NOS inhibitors aggravated them. These biological changes after RS were associated with lowered levels of NO metabolites (NOx) in plasma and brain tissue.. The results from our experiments suggest that stress susceptibility and adaptation are regulated by NO, and results with exogenous NO modulators, endogenous NO markers, as well as NO metabolites, point towards this hypothesis. It appears that NO could also act as an endogenous adaptogen and also act as a potential target molecule for drug development in stress and stress related disorders.

IL72. Nitric Oxide and Oxidative Stress in Experimental Models of Excitotoxicity

Mumedy Swamy, K. N .S. Sirajudeen, Zulkarnain Mustapha, Wan Roslina Wan Yusof, Mohd Jamsani Mat Salleh and Chandran Govindasamy

Department of Chemical Pathology, School of Medical Sciences, Health campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia Email:mswamy@kb.usm.my

Neuronal excitation involving the excitatory glutamate receptors is recognized as an important underlying mechanism in neurodegenerative disorders. Nitric oxide (NO) is postulated to be involved in the pathophysiology of many epilepsy models resulting from increased action of excitatory neurotransmitter namely glutamate. NO is synthesized from arginine by nitric oxide synthase (NOS), and the citrulline generated as a by-product can be recycled to arginine by argininosuccinate synthetase (AS) and argininosuccinate lyase (AL) via the citrulline-nitric oxide cycle. The conversion of glutamate to glutamine by glutamine synthetase (GS), which takes place

within the astrocytes represents a key mechanism in the regulation of excitatory neurotransmission under conditions as well as in injured brain. Reactive Oxygen Species (ROS)/Reactive Nitrogen Species (RNS) been implicated in the pathogenesis of various neurological disorders including epilepsy. The exact mech contributing to increased production of NO in excitotoxicity are not well established. The acute ammonia in brain, epilepsy and hypoxia & reperfusion injury to brain are few of the conditions where excitotoxicity ha implicated. To understand the role of NO and oxidative stress in excitotoxicity in the experimental rat m of acute ammonia toxicity, kainic acid mediated epilepsy and anoxia (hypobaric hypoxia) & reperfusion, t concentration [estimated as nitrate/nitrite (NOx)], the enzymes of citrulline- NO cycle, the activity of glut synthetase, the concentration of Thiobarbituricacid reactive substances (TBARS) and Total Antioxidant S (TAS) were assayed in their cerebral cortex (CC), cerebellum (CB) and brain stem (BS). All our experimental m clearly demonstrated the increased formation of NO and support the involvement of NO in the pathophysi of excitotoxicity. The increased activities of AS and AL indicate the effective recycling of citrulline to arginine suggest a functional role to citrulline –NO cycle enzymes in excitotoxicity. The decreased activity of GS in the b regions indicate the modulation of its activity by NO and favors the prolonged availability of glutamic acid cau excitotoxicity leading to neuronal damage. The increased concentration of TBARS and decreased concentratio TAS supports the involvement of oxidative stress in excitotoxicity and suggests a potential for the role of antioxi therapy in preventing neurodegeneration in excitotoxicity.

IL73. Formation of Bio-Active Nitric Oxide Species in Circulation

Enika Nagababu, Maria Salgado and Joseph M. Rifkind

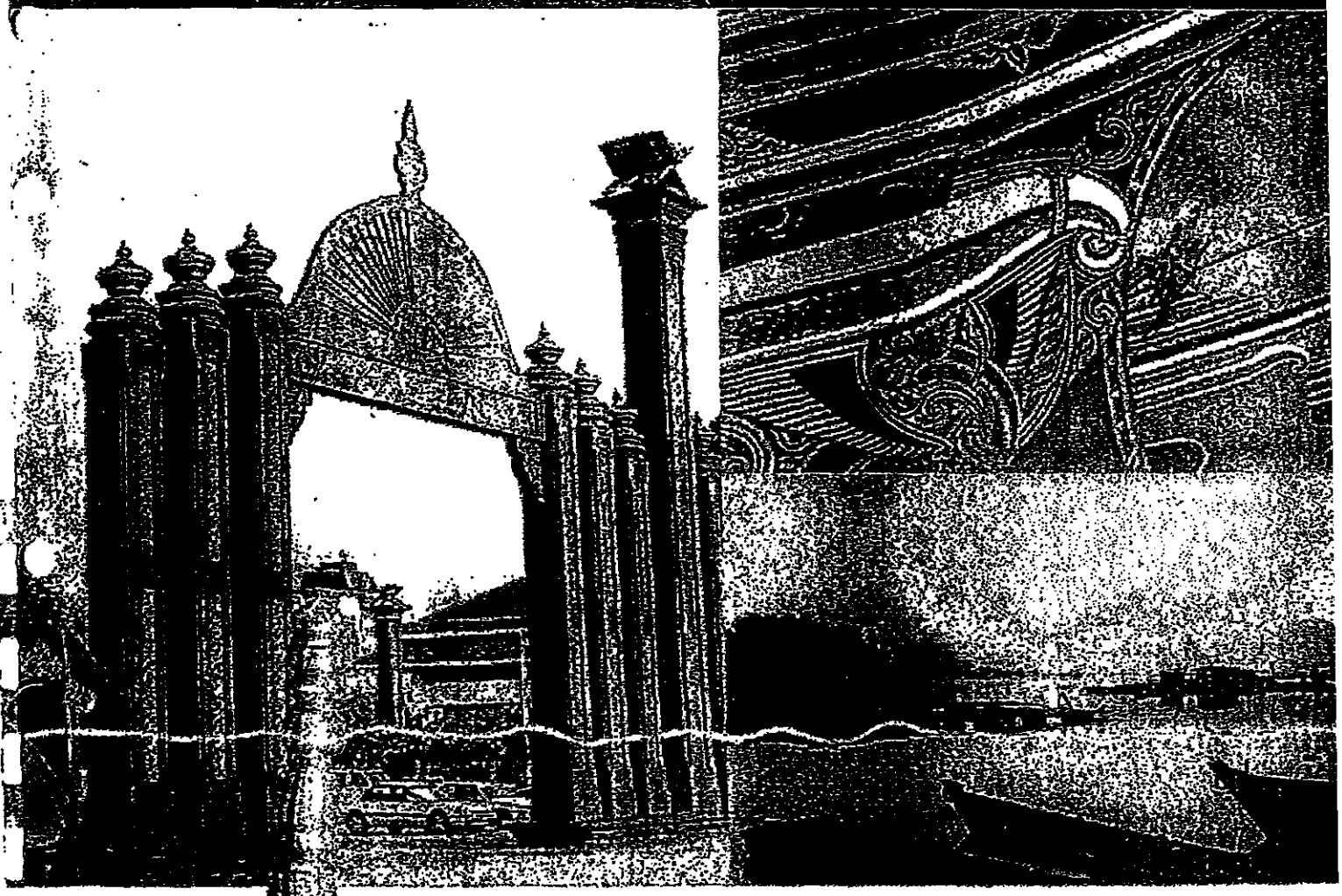
Molecular Dynamics Section, National Institute on Aging, National Institutes of Health, 251 Bayview Blvd, Baltimore, MD. 21224
Email:EnikaN@grc.nia.nih.gov

Nitric oxide that diffuses into circulation from endothelial cells converts to nitrite and S-nitrosothiols (SNO), which are present in plasma in nanomolar concentrations. Both nitrite and SNO have vasodilatory activities that protect against hypertension and cardiovascular diseases. This activity requires that nitrite is converted to nitric oxide (NO). The nitrite reductase activity of deoxyhemoglobin (deoxyHb) is one of the predominant mechanisms to reduce nitrite to NO. However, it is not understood how NO generated in the red blood cells escapes from the scavenging activities of deoxyHb. In order to understand this mechanism, the reduction pathway of nitrite by deoxyHb was investigated and two intermediate species (Hb(II)NOOH and Hb(II)NO+ ↔ Hb(III)NO) were identified prior to the formation of the final product, Hb(II)NO. These intermediate species have a longer life-span in presence of deoxyHb than NO and have high affinity to the membrane. We in fact observed the binding of nitrite reacted Hb to RBC membranes that results in the release of NO into the gas phase. Based on these observations, we proposed that association of intermediate species that are formed during the reaction of nitrite with deoxyHb facilitates the release of NO from RBCs to the vasculature. The mechanism for the formation of the second bioactive species, SNO in circulation was also investigated. NO does not directly react with thiols to form SNO. However, NO+, an oxidized form of NO can react with thiols to form SNO. NO is known to interact with metalloproteins to form NO+ by reducing oxidized metals. Thus, we proposed that the reaction of NO with metal compounds that are already coordinated with thiol groups may generate SNOs. Hemin- Fe(III) and thiol complexes exist in red blood cells and in plasma. Therefore, reactions of NO with hemin and GSH-hemin complexes were investigated. The results show that NO alone does not reduce hemin to heme- Fe(II). However, hemin reduction, heme nitrosylation and S-nitrosoglutathione formation were observed when NO is added to GSH-hemin complex under anaerobic conditions. The reaction of NO with albumin-hemin complex or GSH-hemin complex incorporated membranes also generates S-nitrosothiols. These results provide a mechanism for SNO formation in circulation.

8TH

ANNUAL SCIENTIFIC MEETING & ANNUAL GENERAL MEETING OF THE COLLEGE OF PATHOLOGISTS, ACADEMY OF MEDICINE, MALAYSIA

6 -7 JUNE 2009 RENAISSANCE KOTA BHARU HOTEL



PROGRAM BOOI

THE USEFULNESS OF NEUTROPHIL CD 64 EXPRESSION IN DIAGNOSIS OF NEONATAL SEPSIS

Authors: **Azma R Z**, Noraesah M, Roshidah H*, Irene GS Cheah#, Ainoon O
Department of Pathology, Faculty of Medicine, UKM.

BACKGROUND: Neonatal sepsis is a significant cause of neonatal morbidity and mortality. It is well known that the signs of neonatal bacterial sepsis are often non-specific and may be clinically indistinguishable from those non-infectious conditions. The diagnosis of neonatal sepsis using blood culture would cause delayed in starting antibiotic therapy. Neutrophil CD64 upregulation is induced by inflammatory-related cytokoines. The aim of this study was to study the usefulness of neutrophil CD 64 expression in the diagnosis of neonatal sepsis in our hospital population.

MATERIALS AND METHOD: Peripheral blood samples from 39 term and preterm neonates admitted in the Special Care Nursery in Maternity Hospital HRL, which were suspected for sepsis, were recruited to this study. In addition to routine septic workout, 50-100 µl of blood was collected in EDTA tube to determine CD64 expression by flow cytometry. The suspected neonates were classified into two groups; septic group (n=6), neonates who had positive blood culture with clinical signs and symptoms, and in non-septic group (n=33), the neonates had clinical symptoms and signs but negative blood culture. Additional 18 neonates who were admitted for jaundice, which were monitored without evidence of sepsis were classified as control group.

RESULTS: Results showed increased CD64 expression in septic group. The differences of CD64 expression among three groups were statistically significant ($P<0.001$). We were able to determine the cut off value of >5628 antibody-PE molecules per cell from ROC curve. This study exhibited moderate sensitivity (83%) with high negative predictive value (95%). However, CD64 expression had an intermediate specificity (61%) for neonatal sepsis and low positive predictive (28%) value. There was also an increased CD64 expression in clinical pneumonia. However, there was poor correlation between neutrophil CD64 and absolute neutrophil count ($r=0.009$).

CONCLUSION: In conclusion, CD64 appear to be a sensitive marker in neonatal sepsis. The rapidly availability of the laboratory results would help neonatologist in the management of the neonates with sepsis

NITRIC OXIDE, GLUTAMINE SYNTHETASE AND OXIDATIVE STATUS IN DIFFERENT REGIONS OF BRAIN IN RAT SUBJECTED TO ANOXIA (HYPOBARIC HYPOXIA)

Authors: **Mohd Jamsani Mat Salleh**, M. Swamy, Wan Rosina Wan Yusof, K. N. S. Sirajudeen and Chandran Govindasamy
Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia.

INTRODUCTION: Reactive oxygen species (ROS) have been implicated in pathophysiology of many neurological disorders and brain function. Nitric oxide is postulated to be involved in the pathophysiology of neurological disorder due to hypoxia/ anoxia generated ischemia in brain due to increased release of glutamate and activation of N-methyl-D-aspartate receptors (NMDA receptors). To understand the NO production and its involvement in modulation of glutamine synthetase (GS) activity along with oxidative status in anoxia (nitrate /nitrite (NOx), GS, lipid peroxidation products as thiobarbituric acid reactive substances (TBARS) and total Antioxidant Status (TAS) were analyzed in cerebral cortex (CC), cerebellum (CB) and brain stem (BS) of rats subjected to anoxia.

METHODOLOGY: Anoxia was induced in adult male Sprague Dawley rat (test group) by keeping in a desiccator connected to a vacuum pump and the air was removed producing hypobaric conditions as per the procedure of Sadasivudu & Swamy. The rats were killed by decapitation. Control group of rats were free access to food and water and killed by decapitation. From both groups of rats the brain regions (CC, CB and BS) were separated and homogenized. In the homogenates Nitrate/Nitrite, GS, TBARS and TAS were assayed spectrometrically. Statistical analysis was done by using independent student t-test.

RESULTS: NOx and TBARS concentrations were increased and GS activity and TAS were decreased significantly in all the brain regions tested in rats subjected to anoxia compared to control group.

CONCLUSION: The results of this study clearly demonstrate the involvement of NO in the pathophysiology of anoxia as well as in the decreased activity of GS. The decreased activity of GS may be for the prolonged availability of glutamic acid for excitotoxicity which leads to neuronal damage in anoxia. The increased formation of TBARS and decreased TAS indicates the presence of oxidative stress in anoxia (hypobaric hypoxia).

International Journal of Medical Sciences

3 March 2010

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Mummedy Swamy

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IJMS Editorial Team
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Manuscript information

Submission type: revision 1714c

Manuscript title: NITRIC OXIDE (NO), CITRULLINE – NO CYCLE ENZYMES, GLUTAMINE SYNTHETASE AND OXIDATIVE STRESS IN ANOXIA (HYPOBARIC HYPOXIA) AND REPERFUSION IN RAT BRAIN

Manuscript author(s): M. Swamy*, Mohd Jamsani Mat Salleh, K. N .S. Sirajudeen, Wan Roslina Wan Yusof and G. Chandran

Submitting author name: Dr. Mummedy Swamy

Contact email: mswamy@kb.usm.my

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Manuscript category: Research paper

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2. Prof. Sivachandra Suraparaju, shivachandra@hotmail.com

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IJMS Editorial Team
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Submission type: new

Manuscript title: NITRIC OXIDE (NO), CITRULLINE - NO CYCLE ENZYMES, GLUTAMINE SYNTHETASE AND OXIDATIVE STRESS IN ANOXIA (HYPOBARIC HYPOXIA) AND REPERFUSION IN RAT BRAIN

Manuscript author(s): M. Swamy*, Mohd Jamsani Mat Salleh, K. N .S. Sirajudeen, Wan Roslina Wan Yusof and G. Chandran

Submitting author name: Dr. Mummedy Swamy

Contact email: mswamy@kb.usm.my

Additional email or contact info (optional): mummedys@yahoo.co.in

Manuscript category: Research paper

Suggested reviewers: 1. Prof Zheng-hong Qin, zhqin5@hotmail.com

2. Prof. Sivachandra Suraparaju, shivachandra@hotmail.com

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NITRIC OXIDE (NO), CITRULLINE – NO CYCLE ENZYMES, GLUTAMINE SYNTHETASE AND OXIDATIVE STRESS IN ANOXIA (HYPOBARIC HYPOXIA) AND REPERFUSION IN RAT BRAIN

M. Swamy*, Mohd Jamsani Mat Salleh, K. N .S. Sirajudeen, Wan Roslina Wan Yusof and G. Chandran

Department of Chemical Pathology, School of Medical Sciences, Health campus,

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Running title:
NO and oxidative stress in anoxia & reperfusion

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ABSTRACT

Nitric oxide is postulated to be involved in the pathophysiology of neurological disorders due to hypoxia/ anoxia in brain due to increased release of glutamate and activation of N-methyl-D-aspartate receptors. Reactive oxygen species have been implicated in pathophysiology of many neurological disorders and in brain function. To understand their role in anoxia (hypobaric hypoxia) and reperfusion (reoxygenation), the nitric oxide synthase, argininosuccinate synthetase, argininosuccinate lyase, glutamine synthetase and arginase activities along with the concentration of nitrate /nitrite, thiobarbituric acid reactive substances and total antioxidant status were estimated in cerebral cortex, cerebellum and brain stem of rats subjected to anoxia and reperfusion. The results of this study clearly demonstrated the increased production of nitric oxide by increased activity of nitric oxide synthase. The increased activities of argininosuccinate synthetase and argininosuccinate lyase suggest the increased and effective recycling of citrulline to arginine in anoxia, making nitric oxide production more effective and contributing to its toxic effects. The decreased activity of glutamine synthetase may favor the prolonged availability of glutamic acid causing excitotoxicity leading to neuronal damage in anoxia and reperfusion. The increased formation of thiobarbituric acid reactive substances and decreased total antioxidant status indicate the presence of oxidative stress in anoxia and reperfusion. The increased arginase and sustained decrease of GS activity in reperfusion group likely to be protective.

Key words: Citrulline – Nitric oxide cycle; Nitric oxide; Anoxia; Hypobaric hypoxia; Reperfusion; Excitotoxicity; Glutamine synthetase; Thiobarbituricacid reactive substances; Total antioxidant status