OXYGEN DERIVED FREE RADICALS AND TISSUE INJURY

Essay

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By

Medhat Magdy Kamel
(M.B., B. CH.)
Faculty of Medicine Ain Shams University

Under Supervision of

Prof. Dr. Hany Sobhy Rufail
Professor of Clinical Pathology
Faculty of Medicine Ain Shams University

Dr. Ola Hamdy Demerdash
Lecturer of Clinical Pathology
Faculty of Medicine Ain Shams University

Dr. Dalia Helmy Farag
Lecturer of Clinical Pathology
Faculty of Medicine Ain Shams University

Faculty of Medicine
Ain Shams University
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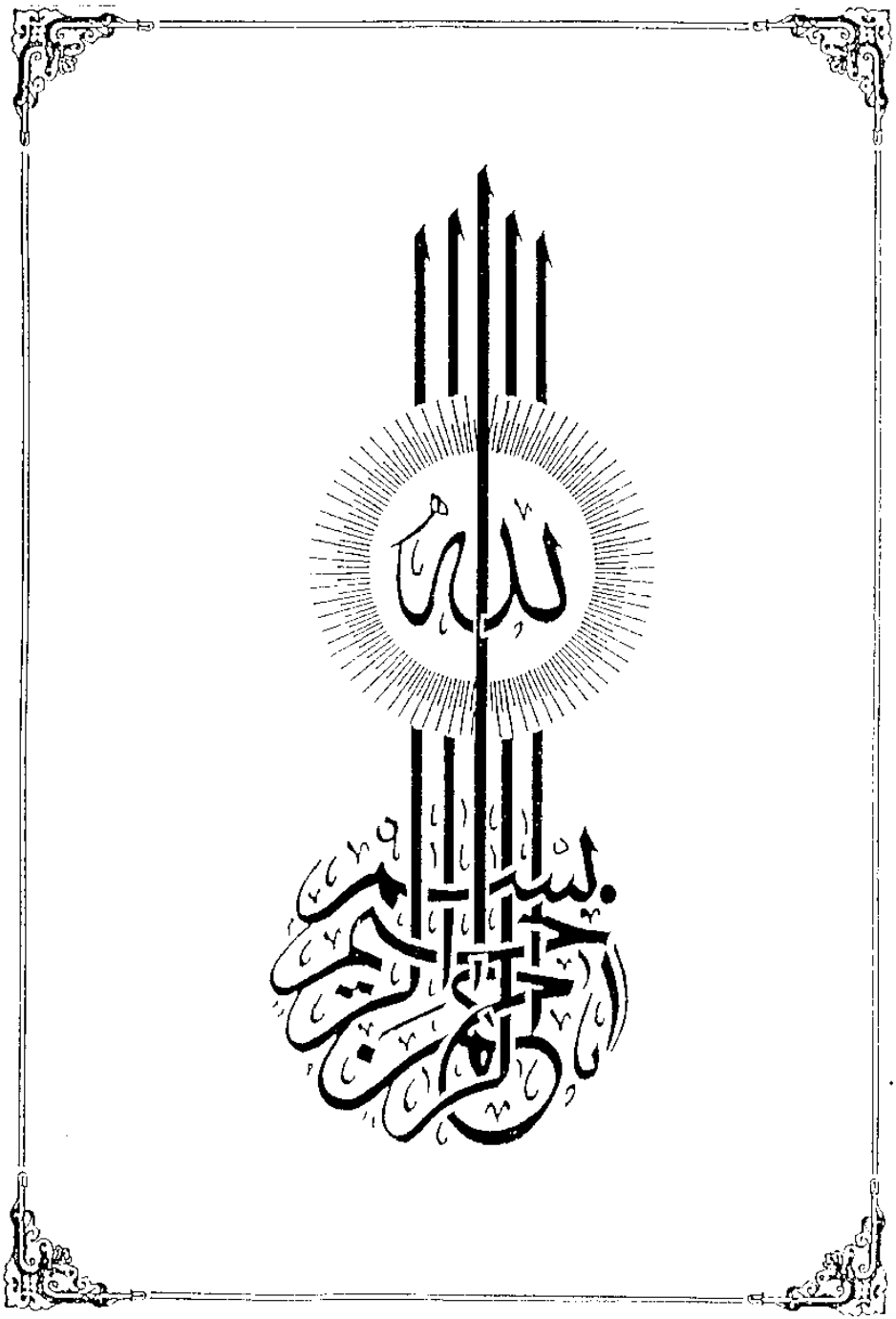

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List of Abbreviations

ADP :	Adenosine diphosphate .
Alpha PI :	Alpha - proteinase inhibitor .
ATP :	Adenosine triphosphate .
BHA :	Butylated hydroxyanisole .
BHT :	Butylated hydroxytoluene .
CAR :	Bcarotene .
cl :	Chloride .
cu :	Copper .
DNA :	Deoxyribonucleic acid .
DPPP :	Diphenyl - 1 - pyrenyl phosphine .
DTNB :	Dithiobis , 2- nitrobenzoic acid .
e⁻ :	Electron .
EDTA :	Ethylene diamine tetra - acetic acid .
Fe :	Iron .
Fig :	Figure .
GSH :	Reduced Glutathione .
GSSG :	Oxidized Glutathione .
GSH - Px :	Glutathione peroxidase .
H^+ :	Hydrogen ion .
Ho· :	Hydroxyl radical .
H_2o :	Water .
H_2o_2 :	Hydrogen peroxide .
Ho_2· :	Perhydroxyl radical .

HoBr :	Hypobromus acid .
HocL :	Hypochlorous acid .
Hol :	Hypoiodus acid .
HoscN :	Hypocyanous acid .
Hox :	Hypohalous acid .
HPLC:	High - performance liquid chromatography .
MDA :	Malondialdehyde .
Mn :	Manganese .
NAD^+ :	Nicotinamide adenine dinucleotide .
NADH :	Reduced Nicotinamide adenine dinucleotide .
$NADP^+$.	Nicotinamide adenine dinucleotide phosphate .
NEM :	N - ethylmaleimide .
nm :	Nanometer .
O_2 :	Oxygen .
$O_2^{-\cdot}$:	Superoxide radical .
O_2^1 :	Singlet oxygen .
ΔO_2^1 :	Delta form of singlet oxygen .
ΣO_2^1 :	Sigma form of singlet oxygen .
OH^- :	Hydroxyl anion .

Plase A_2 :	Phospholipase A_2 .
PLooH :	Phopholipid hydroperoxides .
PUFA :	Polyunsaturated fatty acid .
R· :	Alkyl radical .
RH :	Fatty acid .
Ro· :	Alkoxy radical .
RoH :	Fatty acid alcohols .
Roo· :	Peroxy radical .
RNA :	Ribonuclice acid .
Se - GSH - Px :	Selenium glutathione peroxidase .
SOD :	Superoxide dismutase .
SQ :	Semiquinone .
SQ· :	Semiquinone free radical .
TBA :	Thiobarbituric acid .
Q :	Quinone .
UV :	Ultra violet .
UQHZ :	Reduced co enzyme Q .
X· :	Reactive oxidant .
X^- :	Halides .

INTRODUCTION

INTRODUCTION

Recent attention has been focused on the role of oxygen derived free radical in disease. In circumstances of tissue injury , it is currently popular to incriminate such by products of oxygen metabolism as the ultimate injurious agents (Menasche and Piwnica , 1989).

There is what is known as oxidant - antioxidant balance inside the body , where the effect of these free radicals is blocked by cellular antioxidants and free radical scavengers . When the oxidant-antioxidant balance is disrupted , the toxicity of these radicals becomes unopposed and they cause injury to membrane lipids , proteins , nucleic acid and extracellular matrix (Machlin and Bendich , 1987).

The aim of this work is to give a detailed account on oxygen derived free radicals and the mechanisms of free radical mediated tissue injury. Included also is a discussion of the methods for detection of free radical .

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

I. OXYGEN DERIVED FREE RADICALS

A free radical is any molecule that has an odd number of electrons in its outer orbit .The presence of the odd electron makes the free radical species highly reactive , transient and potentially cytotoxic (Royston , 1988) .

Free radical result from symmetrical cleavage of the shared electrons of a covalent bond

$$A:B \rightarrow A. + B.$$

The high reactivity is due to the strong tendency of the unpaired electron to interact with other electrons to form an electron pair and thus chemical bond . Consequently , the free radical half life is low (Henson and Johnston , 1987) .

According to the classification proposed by Del Maestro (1980) , radical reactions can be divided into three phases : initiation , propagation , and termination . These reactions tend to occur as "chain reactions" i.e. involving a series of passages , each of them forming a free radical which triggers the next step .

In the initiation phase , energy is absorbed which leads to the formation of the free radicals . This may be initiated during oxidation - reduction reactions (Pryor , 1976) .

The propagation phase is characterized by reactions , in each of them a free radical is consumed and another is formed . The process of radical propagation is responsible for most of the damaging effects of free radicals and it can continue indefinitely or can be terminated by a variety of free radical scavenging species (Freeman and Crapo, 1982) .

The termination phase is the step by which the chain propagation closes and during which the other radicals are recombined . The chain reactions , therefore, are self - perpetuating process with formation of new radicals in the stage of propagation , so that each primary radical formed in the initial stage may give to thousands of molecules produced (Del Maestro , 1980) .

A- Types and Formation of Oxygen Derived Free Radicals

Oxygen is a strong oxidant but it is a relatively unreactive compound that can be metabolised in vivo to form highly reactive derivative oxidants . Molecular oxygen (o_2) contains two unpaired electrons in its outer orbital . These electrons have parallel spins (↑)(↑) .This is known as ground state diatomic oxygen and it should have the symbol o_2·· but written o_2 for simplicity . If the oxygen molecule is to take part in a chemical reaction to oxidize another atom or molecule , it accepts two further electrons from it to fit into the vacant spaces in the orbitals . The additional electrons must spin in the opposite direction to those already in place to fulfill the requirements of the natural laws of physics and chemistry , and so the final configuration is (↑↓)(↑↓) . As most biomolecules are covalently bonded non radicals , and the two electrons forming a covalent bond have opposite spins and occupy the same molecular orbital . Hence the reaction of oxygen with biomolecules is spin restricted (Royston , 1988 ; Halliwell and Gutteridge , 1990) .

In presence of catalyst oxygen can oxidize biologically relevant two electron donor molecules at rapid rates . In vivo enzymes are able to complex oxygen and substrate molecules for sufficient lengths of time to allow these oxidations to occur . The best example of this type of enzyme is the mitochondrial enzyme cytochrome oxidase whereby oxygen receives four electrons and is reduced directly to water .

There are two other enzymes capable of catalyzing oxygen - dependant oxidation reactions ; the xanthine oxidase of capillary endothelial cells and the NADPH oxidase of human phagocytes. In both of these enzyme systems , oxygen can be reduced to form a group of highly reactive oxygen metabolites capable of damaging the microcirculation (Royston , 1988) .

Although oxygen can accept a total of four electrons to form H_2O , it can be reduced in univalent steps to generate three types of reactive intermediates as in Fig (1) .

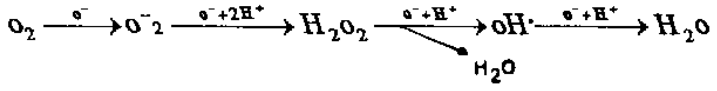

Fig 1. The univalent pathway for reduction of molecular oxygen .
(Del Maestro , 1980)

The addition of a single electron to oxygen molecule results in the formation of superoxide radical ($o_2^{-\cdot}$) .The additional negative charge denoted by the electron gives the oxygen molecule a net charge of - 1 (hence an anionic species) , while the presence of a single unpaired electron is denoted by the single dot (Royston , 1988) .

O_2(16 protons , 16 electrons , no charge , biradical) $(\uparrow)(\uparrow) + e^- \longleftrightarrow o_2^-$ (16 protons , 17 electrons , negative charge, free radical) $(\uparrow)(\downarrow\uparrow)$

Then the next stage of electron acceptance is

$$o_2^{-\cdot} + e^- \longleftrightarrow o_2^{2-}$$

(16 protons , 18 electrons , 2 negative charge , not a radical)

(↑↓)(↑↓)

$o2^{2-}$ ion is termed the peroxide species and at physiological pH it is protonated to produce hydrogen peroxide (H_2o_2) , an electrically natural, stable compound .

$$o_2^{2-} + H \longleftrightarrow Ho_2^-$$
$$Ho_2^- + H \longleftrightarrow H_2o_2$$

Next , the addition of an electron to H_2o_2 (a total of 3 electrons to oxygen), leads to the formation of the hydroxyl radical (Ho.)

$$H_2o_2 + e^- \longleftrightarrow Ho. + oH^-$$

Finally , the addition of the fourth electron to Ho. reduces this species to the hydroxyl anion (oH^-) .

$$Ho. + e^- \longleftrightarrow oH^-$$
$$2oH^- + 2H \longleftrightarrow 2H_2o$$