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Editorial

Free Radicals are dutiful soldiers, no more to be spared as bio-terrorists

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If we analyse the increasing beneficial roles so far explored as being played by free radicals and their deliberate enzymatic generation when requied, one can very well presume their generating pathways as inteligently designed systems already existing for maintaining normal health. On the other hand, free radicals, if produced in excess because of various unwanted exogenous factors,they begin to covet their neighbouring molecules' electrons and by stealing electrons, they operate as terrorists by producing diseases in the body. The idea of constructing this title of the editorial came suddenly to the mind of the author after having a glimpse of a very recent article (Dec 2016), the main cotent being the emergence of molecular hydrogen as top ranking antioxidant.possesing the full potentiality of minimizing excssively generated free radicals upto its physiological level.

Before jumping directly on to those documented facts and other reports for support of the title of the editorial, let us have a briefing on free radicals to refresh the knowledge we conceived earlier. Free radicals are those molecular species capable of independent existance, each containing an unpaired electron in one of their atomic orbitals, hence very reactive and short-lived. Some species without unpaired electrons like, singlet oxygen, hydrogen peroxide etc. which can easily be transformed to the most reactive species have also been taken in as their members under a class known as reactive oxygen species (ROS). Thus, we have two groups of free radicals namely, (1) reactive oxygen species (ROS) and (2) reactive nitrorgen species (RNS). Reactive oxygen species are partially reduced derivatives of molecular oxygen and in this group, we have Singlet **oxygen ($^1O_2$), Superoxide anion radical ($\cdot O_2^-$), hydroxyl radical ($^{\cdot}OH$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl**) etc as its important members. **Hydroxyl radical (OH$\cdot$)** and **hypochlorous acid (HOCl**) are the most reactive members directly involved in damaging tissues or molecules. **Nitric oxide ($\cdot NO$**) is the mother molecule of RNS, the other members of this group namely, **nitrous oxide (N_2O), Peroxy nitrite ($^{\cdot}OONO$), nitrogen dioxide ($\cdot NO_2$), nitroxyl anion (HNO), peroxy nitrous acid (HNO_2**) etc are all derivatives of **$\cdot NO$. Peroxynitrite (OONO**) is the most reactive nitrogen species which can direcly react with various biological target molecules.

Endogenous sources of free radicals are **(a)NADPH oxydase, being an enzyme dedicated for generation of ROS** in mammalian cells from NADPH as its substrate **(b) Nitric oxide synthase** (NOS), also being an enzyme dedicated for synthesis of nitric oxide ($\cdot NO$), the mother molecule of RNS, the substrates being Arginine and molecular oxygen, **(c)Energy pathways**, mitochondrial electron transport chain being the most delicate site of energy pathway where highest quantity of superoxide anion radical can be generated, **(d) Oxidases**, utilising molecular oxygen as co-factor, most of the time being associated with the production of H_2O_2,**(e)Exercise,** because of increased flow of oxygen,in the skeletal muscle, folowed by increased ETC and xanthine oxidase activity.**(f)**.**Peroxysomes** being organelles producing

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H_2O_2 as byproducts of degaradation of fatty acids and other molecules in it..Free radicals generated by the endogenous pathways, if maintained at its physiological levels, are always found to be engaged in beneficial pathways.

Free radicals: To be treated as dutiful soldiers This first part of the title of the editorial can now be supported by the following few crucial roles, documented as being played by endogenously generated free radicals. **(1) Defence against foreign invaders:** Our body harnesses the most dangerous free radicals for use in the immune system for defence against pathogens. Certain cells like neutrophills, macrophages etc, engulf bacteria or viruses and creats the most powerful free radicals like hypochlorous acid (HOCl) or hydroxyl radical (OH) by taking up molecular oxygen (O2) rapidly from the blood for bombarding the pathogens. NADPH oxidase play the dmnant role in producing the initial ROS

$$2O_2 + 2\ NADPH \xrightarrow{NADPH\ \ Oxidase} 2 \cdot O_2^- + NADP + H+$$

$$2 \cdot O_2^- + 2H^+ \xrightarrow{Superoxide\ -dismutase} H_2O_2 + O_2$$

$$H_2O_2 + Cl- + H^+ \xrightarrow{Myloperoxidase} HOCl + H_2O$$

$$H_2O_2 + Fe++ \xrightarrow{Fanton\ reaction} \cdot OH + OH^- + Fe+++$$

(2) NO as signalling agents: The most well-known free radical acting as signalling molecule is ▪ NO. Three isoforms of NOS are available for synthesis of three ▪ NO radicals having different signalling characters. The gene for NOS-1 or nNOS(neuronal NOS) is located in chromosome no. 12. The role of NO synthesised by NOS-1 works for cell to cell communication. The gene for NOS-2 or iNOS(inducible NOS) is located in chrosome no.17 and ▪ NO synthesised by it is involved in defense against pathogens after conversion to highly reactive free radical namely peroxy nitrite(OONO). The gene for NOS-3 or eNOS (endothelial NOS) is located in chromosome No. 7 in endothelial cells, endocardium and myocardium, in plasma membrane and it is activated by calcium. ▪ NO synthesiized by it is involved in muscle relaxation by using cGMP as its 2nd messanger [1]. **(3) Regulation of sperm function:** Free radicals, at its physiological level, control the maturation, capacitation, hyperactivation, the acrosome reaction (AR) and oocyte fussion of sperms. Lipid peroxidation caused by low level of reactive oxygen species leads to modification of plasma membrane facilitating sperm oocyte adhesion [3]. **(4) Acting as signal substance for regulating heart beat:** When our body is subjected to different types of stress, symphatatic nervous system starts stimulating β adrenergic receptors on the surface of the heart muscle cells leading to contraction of the heart with greater force via activation of certain proteins inside the cells by phosphorylation.It was also found that these β adrenergic receptors, ,when stimulated, caused increased production of free radicals in the mitochondria of the cell and these then contribute to stronger contraction of the cells. This β adrenergic stimulation of heart muscle cell disappeared when exposed to antioxidants showing the real role of free radicals for pumping more blood by the heart in stress filled situations and negative effect of antioxidants [4]. **(5) Regulation of Erythropoietin production**: Production of erythropoietin (EPO), the glycoprotein hormone which control red blood cell formation has already been reported as being regulated by ROS by feedback mechanism. H_2O_2, via production of OH by Fenton reaction, could act as intracellular signalling molecule. High cellular level of H_2O_2 inhibit EPO production while low levels, as under hypoxia, allow full expression [2]. **(6) Enhancement of insulin sensitivity:.**Free radicals induced by exercise enhances insulin sensitivity via activation of free radical dependent trancriptional co-factors and transcription factors. This free radical related induction of transcription factors and transcriptional co-factors, also lead to increased expression of enzyme antioxidants including **superoxide** dismutase-1(SOD 1), superoxide dismutase-2(SOD 2) and glutathion peroxidase, thus, offering an increased protection from

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oxidative stress [6]. **Exogenous** sources of free radicals are (a) Alcohol **consumption**, (b) **Tobacco smoking**, (c) **Ingestion of heavy and transition metal ions, industrial solvants, pesticides** etc (d) **Toxic drugs** while detoxifying by **cytochrome 450** (e**) Exposure to ionizing radiation, ozone, poluted environment hyperoxia** etc. Free radicals produced under exogenous conditions, always intends to overwhelmed body's ability to regulate them ultimately leading to a condition known as oxidative stress. All aerobic forms of life, as such, maintained an elaborate antioxidant system as its own defense squad; enzymes like superoxide dismutase (SOD), catalase and glutathione peroxidase and non-enzymic molecules like glutathione ,uric acid, allopurinol etc, being its membersnt squad fails to counteract the increasing load of free radicals, because of their attack on DNA, protein, and lipids in the body,the consequeces will be the appearance of diseases like,cancer, atheroschlerosis, heart disease, cardiovascular disease, stroke, emphysema, diabetes mellitus, rhumatoid athritis , osteoporosis, ulcers, sun burn, cataract, Crohn's disease, aging etc. Under such conditions, antioxidant therapy will be the only option but, despite the current wealth of knowldge on exogenous antioxidants, there was much skepticism regarding the likelihood of a complete success with the so far existing standards of antioxidant therapy.

Free radicals: no more to be spared as biological terrorists As cited above, this last part of the title of the editorial was inserted after getting sufficient supportive information from Lei Huang's recent article, appeared in Medical Gas Research 2016 [7], the impotant information being about **molecular hydrogen appearing** as the most promising antioxidant which could be used both for preventive and therapeutic treatment of almost all types of free radical linked diseases. The underlying comprehensive mechanism of this gas is beyond hydrxyl radical scavenging. Uptodate clinical application of this gas to human patient conducted so far, also revealed the safety and promising benefits in varieties of diseases. The commendable characteristics of **molecular hydrogen** they have discovered,ensuring the feasibility and readiness of its clinical translation to human patients are (a) nontoxicity even at very high concentrtion, (b) diffusibility into the subcellular compartments to reduce the cytotoxic oxy- radicals, (c) mild nature, neither disturbing metabolic redox reactions nor affectng signalling ROS , (d) ability to act selectively on the most reactive hydroxyl radical, (e) regulating gene expression, (f) acting as noble signalling molecule , (g) triggering the activation or upgradation of the endogenous antioxidant enzymes, (h) ability to cross blood brain barrier (i) and its capability of imparting the highest antioxidant dose.

Conclusion: So long the concentration of the free radicals generated endogenously remain maintained at its physiological level, almost all of them will remain engaged in body's beneficial activities. Slight excess if any, will also be taken care of by the antioxdant squad created endogenously. But, because of our own ignorance or negligence, if we keep on indulging or exposing ourselves to those unwanted exogenous conditions mention above, oxidative stress will automatically be developed due to the extra load of free radicals, the concequence of which being, the appearance of different diseases. Under such condition, interuption by antioxidant therapy may be the only option. Till now, this effort of trial with antioxidant therapy is going on without much significant response except for a very few cases. However, after this recent discovery of molecular hydrogen as the best antioxidnt tested so far, a new hope suddenly emerges, with full confidence of overcoming all the obstacles being faced while conducting clinical trials of different antioxidants. I wish all the researchers working under this project a great success for the sake of those patients still waiting for recovery. As such, as per the message from Molecular Hydrogen Foundation

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(MHF), we can safely start consuming molecular hydrogen (H2) in place other antioxidants, as H2 only reduces excessive oxidative stress and does not interfere with beneficial ROS.

References

[1] Brahm H, Segal MD Melissa J Grimm, A Nazmul H Khan, Wei Han MD and Timothy S, Regulation of innate Med. 53:1 (2012)72 -80.
[2] Nitric oxide synthase from Wikipedia, the free encyclopedia.
[3] W C L Ford "Regulation of sperm function by reactive oxygen species" Human reproduction update, 10 (2004) 381- 385.
[4] Scientists from the Swedish medical university." Free radicals may be good for you" .https/wwwsciencedaily.com (2011).
[5] N A Daghman, G E. Elder, G A Salvage, P C Winter, T R J Lappin, A P Maxwell,"Erythropoietin production: evidence for multiple oxygen sensing pathway" Annals of hematology. 78 (1999) 215-278.
[6] Free radicals: The positive and negative effects on health" www.molecularhydrogenfoundation.org (2016).
[7] Lei Huang MD, Molecular hydrogen: A therapeutic antioxidant and beyond, Med. Gas. Res. 6:4 (2016) 219-222.

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