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# BIOCHEMISTRY OF FREE RADICALS: FROM ELECTRONS TO TISSUES

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**Abstract** Free radicals are chemical species with an unpaired electron in the outer valence orbitals. The unpaired electron makes them paramagnetic (physics) and relatively reactive (chemistry). The free radicals that are normal metabolites in aerobic biological systems have varied reactivities, ranging from the high reactivity of hydroxyl radical ($t_{½} = 10^{-9}$ s) to the low reactivity of melanins ($t_{½}$ = days). The univalent reduction of oxygen that takes place in mammalian organs produces superoxide radicals at a rate of about 2% of the total oxygen uptake. The primary production of superoxide radicals sustains a free radical chain reaction involving a series of reactive oxygen species (hydrogen peroxide, hydroxyl and peroxyl radical and singlet oxygen). Nitric oxide is almost unreactive as free radical except for its termination reaction with superoxide radical to yield the strong oxidant peroxynitrite. Nitric oxide also reacts with ubiquinol in a redox reaction, with cytochrome oxidase competitively with oxygen, and oxymyoglobin and oxyhemoglobin displacing oxygen. Septic shock and endotoxemia produce muscle dysfunction and oxidative stress due to increased steady state concentrations of reactive oxygen and nitrogen species.

**Resumen** ***Bioquímica de los radicales libres: del electrón a los tejidos.*** Los radicales libres son especies químicas con un electrón solitario en un orbital externo de valencia. El electrón solitario los hace paramagnéticos (física) y relativamente muy reactivos (química). Los radicales libres que son metabolitos normales en los organismos aeróbicos exhiben reactividades variadas, que van desde la alta reactividad del radical hidroxilo ($t_{½} = 10^{-9}$ s) a la baja reactividad de las melaninas ($t_{½}$ = días). La reducción univalente del oxígeno que se lleva a cabo en los órganos de los mamíferos produce radicales superóxido a una velocidad aproximada del 2% del consumo de oxígeno. La producción primaria de radical superóxido mantiene una cadena de reacciones de radicales libres que involucra a una serie de especies reactivas del oxígeno (peróxido de hidrógeno, radicales hidroxilo y peroxilo, y oxígeno singulete). El óxido nítrico es casi no-reactivo como radical libre, excepto su reacción de terminación con el radical superóxido que produce al fuertemente oxidante peroxinitrito. El óxido nítrico también reacciona con el ubiquinol en una reacción redox, con la citocromo oxidasa competitivamente con el oxígeno, y con la oximioglobina y la oxihemoglobina desplazando al oxígeno. El shock séptico y la endotoxemia producen una disfunción y un estrés oxidativo en el músculo mediados por un aumento en las concentraciones en estado estacionario de las especies reactivas del oxígeno y del nitrógeno.

**Key words:** free radicals, reactive oxygen species, nitric oxide, peroxynitrite, septic shock

## 1. The Chemistry of Free Radicals

A free radical is a chemical species with an unpaired electron in the outer valence orbitals. Since orbitals are usually filled with a pair of electrons, an alternative and similar definition is that a free radical is a chemical species with an odd number of electrons. The chemical species can be an atom, such as the hydrogen or the chlorine atom, a transition metal, or a molecule in which case the unpaired electron is located in a molecular orbital. The unpaired electron in the outer valence orbital confers a relatively high reactivity to the molecule due to the strong tendency to acquire a second electron in the orbital. However, transition metals with an odd number of electrons and the free radical form of relatively large organic molecules with delocalized electrons, such as melanins or nitric oxides in which the nitrogen atoms is in an aromatic ring, are relatively unreactive and stable.

Free radicals are chemically written with the notation for the chemical species followed by a dot that indicates the unpaired electron. For instance, the hydrogen atom is indicated as $H^{\bullet}$ and the hydroxyl radical as $HO^{\bullet}$. There are two notation ways to place the dot, $HO^{\bullet}$ and $HO^{\bullet}$, the first one is the classic organic and physical chemistry style and the latter one is the more modern biochemical style. In our days, notation follows whatever is easier in the keyboard of the available computer.

Chemically, free radicals are characterized for sustaining free radical chain reactions, a self propagating kind of reactions in which a free radical reactant yields a product that is also a free radical and that reacts producing another free radical. These feed-forward chemical

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TABLE 1.– *Estimated half-lives of free radicals in biological systems*

| Free radical | | $t_{1/2}$ (seconds) |
|---|---|---|
| Hydroxyl radical | $HO^{\cdot}$ | $10^{-9}$ |
| Alcoxyl radical | $RO^{\cdot}$ | $10^{-6}$ |
| Nitric oxide | $NO^{\cdot}$ | 1-10 |
| Peroxyl radical | $ROO^{\cdot}$ | $10^{-1}$ |
| Ubisemiquinone | $UQH^{\cdot}$ | $10^{-2}$-I |
| Melanins | Complex | days |
| Semiquinones (tar) | Complex | days |

processes are known as propagation reactions and are the core of the free radical chain reactions. Classically, free radical reactions are divided in: a) initiation reactions; b) propagation reactions, and 3) termination reactions. In the initiation reactions a free radical is formed from stable non-free radical chemical species ($AB + C \Rightarrow A^{\cdot} + D + E$). In the propagation reactions, a free radical, also called a reaction center, reacts with a stable molecule giving another free radical or reaction center as product ($A^{\cdot} + CD \Rightarrow AC + D^{\cdot}$). In the termination reactions, two free radicals cancel out their unpaired electrons forming a stable product ($A^{\cdot} + B^{\cdot} \Rightarrow A\text{-}B$).

The chemical reactivity of free radicals is determined by the whole molecule bearing the unpaired electron; consequently, reactivity varies greatly in different free radicals. A way of expressing and comparing chemical reactivity is by listing the half-life time ($t_{1/2}$) of the chemical species (Table 1). A short $t_{1/2}$ indicates a high reactivity, and then hydroxyl radicals are the most reactive of the series. It is understood than when $HO^{\cdot}$ is formed it reacts, at diffusion controlled rates and after a few collisions with water molecules, with the first or the second organic molecule that it encounters. Other highly reactive chemical species which are common biological metabolites, or in other words that are produced in normal conditions, have similar reactivities although their are not free radicals. For instance, the electronically excited state of oxygen, singlet oxygen ($^1O_2$) has a $t_{1/2}$ of $5 \times 10^{-6}$ sec and the powerful oxidant peroxynitrite ($ONOO^{\cdot}$) has a $t_{1/2}$ of 0.05-1 sec.

## 2. Oxygen free radicals

The oxygen molecule constitutes about 20% of the atmospheric air and is paramagnetic. Oxygen atoms ($1s^2$, $2s^2$, $2p_x^2$, $2p_y$, $2p_z$) are highly reactive and react themselves to form the oxygen molecule. However instead of forming a pair of $\sigma$-$\pi$ ligand orbitals with the two $2p_y$ and $2p_z$ forming y-y and z-z bonds, the lowest energy configuration is one in which there is a right angle rotation and formation of a z-y $\sigma$ bond; two three electrons bonds are formed between one pair of electrons of one oxygen atom and a single electron of the other oxygen atom. This particular chemical bond was described by Linus Pauling[1] as two three-electron bond to explain the electronic configuration of the oxygen molecule (Fig. 1). Considering the rule of the unpaired electrons, the oxygen molecule is a biradical, but chemically is rather stable and has been described as a sluggish radical. Most of the isolated biomolecules, proteins, DNA, sugars and some lipids are stable for long time in air (20% $O_2$). However, the oxygen molecule in quite reactive to combine with the iron atoms of hemoglobin and cytochrome oxidase (second order reaction constants of $10^7$-$10^8$ $M^{-1}s^{-1}$) to provide the chemical basis for oxygen transport and respiration. The difference between non-catalyzed and catalyzed oxidations is described by Albert Szent-Gyorgi as: "When Tutenkhamon's grave was opened, his breakfast, consisting in wheat grains, was found unoxidized after three thousand years. This represents the non-catalyzed chemical probability. Had His Majesty risen and consumed his meal this would have been burned in no time. This is the catalyzed biochemical probability"[2].

The oxygen molecule with its two three-electron bonds and its biradical character can be reduced by four successive transfers of one electron and the process, advanced by Michaelis[3], is called the univalent reduction of oxygen (Fig. 2). Two of the intermediates, superoxide and hydroxyl are free radicals. Superoxide radicals are dissociated at physiological pH (pK = 4.7) and are, consequently, charged as an anion ($O_2^-$). Chemically, superoxide anion radicals are quite unreactive and biologically behave as a mild reductant reducing the iron moiety of ferritin, cytochrome c and cytochrome oxidase. Moreover, being charged its permeability through biomembranes is highly reduced except for red blood cells that possess a special system for $O_2^-$ transport. Hydroxyl radical is one of the most reactive chemical species and abstracts hydrogen at near diffusion-controlled rates. Hydrogen peroxide is not a free radical and is chemically stable; however in biological systems it is easily cleaved homolytically by transition metals, such

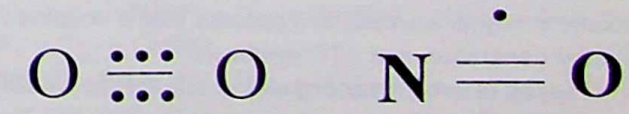

Fig. 1.– Electronic configuration of oxygen and nitric oxide molecules. The lines indicate full covalent bonds with a pair of electrons and the dots indicate single electrons. The oxygen molecule has two three-electrons bonds and is a biradical. The nitric oxide molecule has one single unpaired electron and is a free radical.

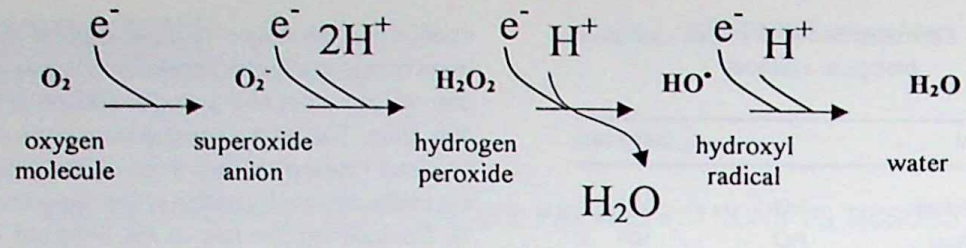


Fig. 2.– The univalent reduction of the oxygen molecule according to Michaelis (1946).

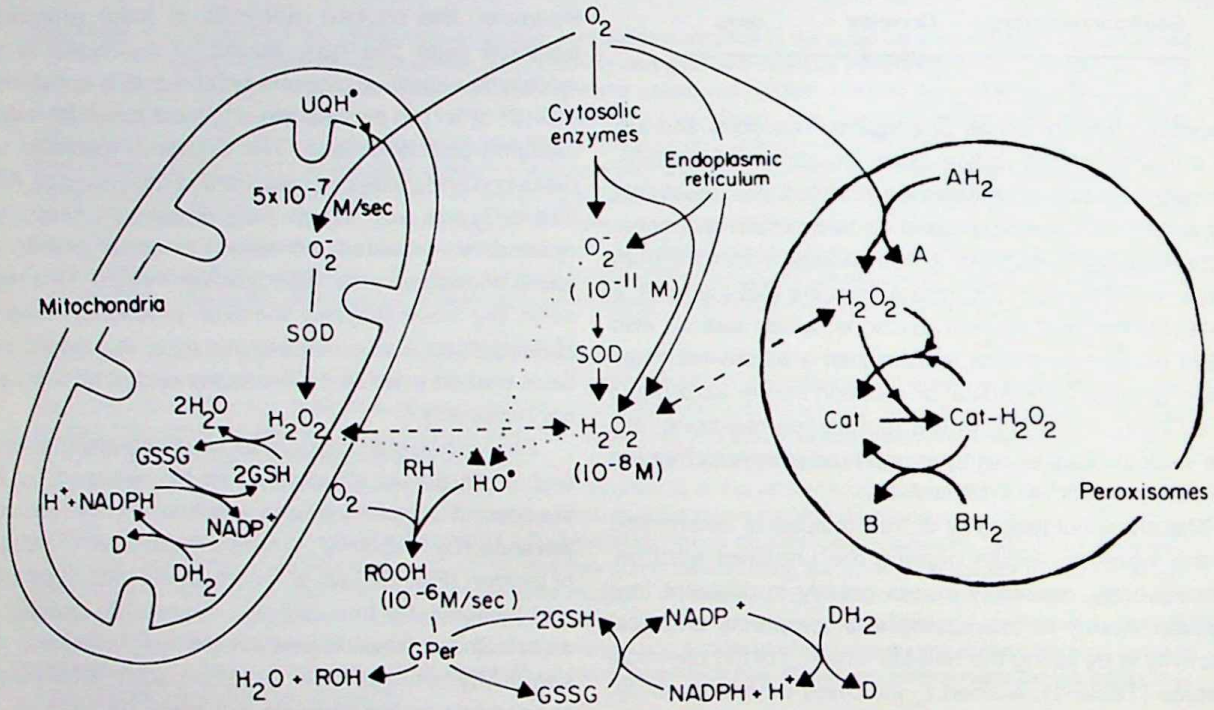


Fig. 3.– Intracellular production of the products of the partial reduction of oxygen. Taken from Chance, Sies and Boveris[4].

as $Fe^{2+}$ and $Cu^{1+}$, to yield hydroxyl radical. Finally, the fourth product of the univalent reduction of oxygen is water. Biological systems that evolved living up with $O_2$ in the atmosphere in the past 3 x $10^9$ years have enzymes that are able to add one, two or four electrons to $O_2$. Water is the stable product of the tetravalent reduction of oxygen carried out by mitochondrial cytochrome oxidase, which accounts for about 97% of the oxygen uptake in higher animals, in a process that is coupled to energy generation and ATP synthesis.

A series of subcellular organelles are able to partially reduce the $O_2$ molecule to $O_2^-$ and $H_2O_2$ (Fig. 3)[4]. The primary production of both products of the partial reduction of oxygen, $O_2^-$ and $H_2O_2$, and the secondary production of $HO^\cdot$ constitute the molecular mechanism of oxygen toxicity[5]. Mitochondria produce primarily $O_2^-$ which dismutates by the enzymatic action of Mn-superoxide dismutase (Mn-SOD) specifically located in the mitochondrial matrix. Endoplasmic reticulum, by autoxidation of the flavoprotein NADPH-cytochrome P-450 reductase and cytochrome P-450, produce both $O_2^-$ and $H_2O_2$. Similarly, other cytosolic enzymes, such as xanthine oxidase, produce both $O_2^-$ and $H_2O_2$. Peroxisomes generate hydrogen peroxide into the peroxisomal core by two-electron transfer from the flavin oxidases to the oxygen molecule. Mitochondria, present in all aerobic cells, are the most important physiological source of superoxide radicals. In hepatocytes, the well developed endoplasmic reticulum affords an equally important source of $O_2^-$ and other subcellular sources are relevant in some cellular types. The semiquinone form of two components of the mitochondrial respiratory chain, ubisemiquinone and the flavin semiquinone of the NADH-dehydrogenase, produce $O_2^-$ by autoxidation in a vectorial

reaction directed to the mitochondrial matrix. Ubisemiquinone autoxidation is known as the Boveris-Cadenas reaction[6-7] and the autoxidation of the flavin seiquinone of NADH-dehygrogenase as the Boveris-Turrens reaction[8]. Superoxide anions are not permeable through the inner mitochondrial membrane and are consequently confined into the matrix where Mn-SOD and NO are the $O_2^-$ co-reactants to yield $H_2O_2$ and $ONOO^-$ as final products, respectively, in a two very fast, diffusion-controlled, reactions. The mitochondrial production of $O_2^-$ accounts for about 2% of the total $O_2$ uptake of perfused rat liver. Similarly, the mitochondrial production of $H_2O_2$ accounts for about 2% of the total $O_2$ uptake of perfused rat liver and heart.

## 3. The nitrogen free radical

Nitrogen molecules account for 79% of the atmospheric air and are formed by two nitrogen atoms, that as free atoms have three unpaired electrons ($1s^2$, $2s^2$, $2p_x$, $2p_y$, $2p_z$) and that form three full covalent bonds ($\sigma$ and 2 $\pi$) in making the stable and inert nitrogen molecule. When a nitrogen atom, with its three unpaired electrons, combines with an oxygen atom, with its two unpaired electrons, the nitric molecule (NO) is formed with an odd total number of electrons. A full N=O double bond ($\sigma$-$\pi$) is formed and an unpaired delocalized electron is left in the molecule that defines the free radical ($NO^\bullet$) character of the NO molecule (Fig. 1). Nitric oxide is a physical free radical in terms of the unpaired electron. The chemical free radical character of NO is restricted; no propagation reactions of $NO^\bullet$ are known to occur in condensed systems but $NO^\bullet$ readily reacts with $O_2^-$ to yield $ONOO^-$ in a classical termination reaction.

## 4. The physiological free radical chain reaction

*4a. The Fenton-Haber-Weiss reactions of oxygen free radicals.* The primary production of $O_2^-$ and $H_2O_2$ is able to initiate and sustain a free radical chain reaction under physiological conditions that encompasses the reactions of lipoperoxidation. Both $O_2^-$ and $H_2O_2$ are the reactants of the initiation process (reactions 1 and 2) in which the reactive $HO^\bullet$ is generated. Reactions 1 and 2 are known as the Fenton-Haber-Weiss chemistry (originally to describe $H_2O_2$ decomposition by iron salts)[4]. Moreover, the biological protective action of superoxide dismutase and catalase is understood as to keep at the slowest rate possible the generation of $HO^\bullet$. The concept has been frequently recognized as the Fridovich dogma[9] of the antioxidant effect of both superoxide dismutase and catalase. Hydroxyl radicals are able to start

$$O_2^- + Fe^{3+} \rightarrow O_2 + Fe^{2+} \quad [1]$$
$$H_2O_2 + Fe^{2+} \rightarrow HO^\bullet + Fe^{3+} + HO^- \quad [2]$$

propagation reactions with unsaturated fatty acids (RH) to yield the stable hydroperoxides (ROOH) (reactions 3, 4 and 5). The peroxyl radicals ($ROO^\bullet$) are able to yield termination reactions with formation of electronically excited products such as singlet oxygen ($^1O_2$) and aldehydes (RHO) and ketones (RO) with excited carbonyl groups(=$CO^*$) (reactions 6 and 7). Reactions 6 and 8 provide, through chemiluminescence, the chemical and molecular basis of an assay to determine the rate of the free radical chain reaction of lipoperoxidation under physiological conditions[10].

$$HO^\bullet + RH \rightarrow R^\bullet + H_2O \quad [3]$$
$$R^\bullet + O_2 \rightarrow ROO^\bullet \quad [4]$$
$$ROO^\bullet + RH \rightarrow R^\bullet + ROOH \quad [5]$$
$$ROO^\bullet + ROO^\bullet \rightarrow RHO + RO + {}^1O_2 \quad [6]$$
$$ROO^\bullet + ROO^\bullet \rightarrow = CO^* + RO + O_2 \quad [7]$$
$${}^1O_2 + {}^1O_2 \rightarrow 2\,O_2 + h\nu \quad [8]$$

*4b. The Beckman-Moncada reactions of nitrogen free radical.* The recognition of the production of $NO^\bullet$ by the nitric oxide synthase (cNOS) of the endothelium as the ERF[11-12] and of the reaction of $O_2^-$ with $NO^\bullet$[13-14] opened a new line of thought in free radical biochemistry. Moreover, the recent discovery of $NO^\bullet$ production by a mitocondrial NOS (mtNOS) located in the inner membrane of rat liver mitochondria[15-17] has started a revolution in terms of both regulation of tissue oxygen uptake[18-23] and of free radical toxicity. Nitric oxide is produced by a series of NOS (cNOS, iNOS, mtNOS) that share the common property of utilizing arginine and $NADPH_2$ as substrates; the reaction is in terms of free radical chemistry and initiation reaction in which the free radical $NO^\bullet$ is produced (reaction 9). The very fast, diffusion-controlled ($k = 6.7 \times 10^9\ M^{-1}.s^{-1}$), termination reaction of the radicals $O_2^-$ and $NO^\bullet$ (reaction 10) is easily understood after considering a collision between the two molecules with unpaired and delocalized electrons that results in bond formation ($ON^\bullet/^\bullet O_2^- \Rightarrow ONOO^-$). Delocalized molecular electrons move thousands times faster than a molecular collision.

$$\text{arginine} + NADPH_2 + O_2 \rightarrow \text{citrulline} + NADP + NO^\bullet \quad [9]$$
$$NO^\bullet + O_2^- \rightarrow ONOO^- \quad [10]$$
$$ONOO^- + RH + H^\bullet \rightarrow NO_2 + H_2O + R^\bullet \quad [11]$$

In addition, $ONOO^-$ has been reported as able to abstract hydrogen atoms from unsaturated fatty acids, acting as a "crypto-$HO^\bullet$" or apparent hydroxyl generator[24] (reaction 11), and to initiate the propagation reactions of lipid peroxidation[25].

TABLE 2.– *Steady state concentrations of reactive oxygen and nitrogen species*

| Species | | Steady state concentration (M) | Tissue/cells/ organelles | Method* |
|---|---|---|---|---|
| Superoxide anion | $O_2^-$ | $2.5 \times 10^{-11}$ | Rat liver cytosol | C |
| | | $0.8 \times 10^{-10}$ | Rat liver mitochondria | M/C |
| | | $1.5 \times 10^{-10}$ | Rat heart mitochondria | M/C |
| Hydrogen peroxide | $H_2O_2$ | $0.5 \times 10^{-8}$ | Rat liver mitochondria | M/C |
| | | $0.6 \times 10^{-8}$ | Rat heart mitochondria | M/C |
| | | $1 \times 10^{-8}$ | Rat liver cytosol | C |
| | | $4 \times 10^{-9}$ | Rat liver peroxisomes | M |
| | | $1 \times 10^{-7}$ | Perfused rat liver | M/C |
| | | $1 \times 10^{-7}$ | Liver cells and slices | M |
| Hydroxyl radical | $HO^\cdot$ | $6 \times 10^{-18}$ | Liver | C |
| Alkyl radical | $R^\cdot$ | $6 \times 10^{-16}$ | Liver | C |
| Peroxyl radical | $ROO^\cdot$ | $2 \times 10^{-9}$ | Liver | C |
| Singlet oxygen | $^1O_2$ | $1 \times 10^{-15}$ | Isolated hepatocytes | M/C |
| | | $1 \times 10^{-16}$ | Liver | M/C |
| Nitric oxide | NO | $5 \times 10^{-8}$ | Liver | C |
| | | $2 \times 10^{-8}$ | Muscle | M |
| | | $1 \times 10^{-7}$ | Rat heart (+ bradikynin) | M |
| Peroxynitrite | $ONOO^-$ | $1 \times 10^{-8}$ | Heart and liver mitochondria | C |

Data taken from ref. 26 for the oxygen reactive species. Data for $NO^\cdot$ from Poderoso's laboratory.
* C: calculated; M/C: production rates measured and steady state calculated; M: measured by diffusion equilibrium

## 5. The steady state concentrations of oxygen and nitrogen reactive species

The steady state approach in which the rate of production of a chemical species is equaled to its rate of utilization or disappearance (*i.e.*, $+ d[O_2^-]/dt = -d[O_2^-]/dt$) and the utilization of the corresponding differential equations allow the estimation of the steady state concentrations of the chemical species. By a combination of measurements and calculations the steady state concentrations of the chemical species participating in the free radical chain reaction of reactive oxygen and nitrogen species are estimated (Table 2).

## 6. The utilization pathways of nitric oxide

Nitric oxide has been recognized to react with a series of relevant biomolecules which are ubiquitous in mammalian tissues and organs. The physiological actions of $NO^\cdot$ would depend ultimately on the relative ratios of the reaction rates of $NO^\cdot$ with the target molecules. In some cases a strong biological effect is to be expected. The reaction of $NO^\cdot$ with $O_2^-$ (reaction 10) is the link between the reactions of oxygen and nitrogen free radicals. However, the rate of $O_2^-$ utilization by this reaction, calculated for rat heart mitochondria under physiological conditions (taking from Table 2 [$3 \times 10^{-8}$ M $NO^\cdot$] and [$1.5 \times 10^{-10}$ M $O_2^-$] and $k = 6.7 \times 10^9$ $M^{-1}.s^{-1}$) results equal to $3 \times 10^{-8}$ M $O_2^-$/sec. This rate is about 30 times slower than the rate of $O_2^-$ utilization by the dismutation reaction. This latter rate can be calculated as $d[O_2^-]/dt = [O_2^-].[SOD].k$ (with [SOD] as $3 \times 10^{-6}$ M and $k = 2.4 \times 10^9$ $M^{-1}.s^{-1}$) and it equals $1.1 \times 10^{-6}$ M $O_2^-$/sec.

There are five important metabolic reactions that utilize $NO^\cdot$ in heart and muscles; three of the reactions occur in the mitochondria: a) with cytochrome oxidase (reaction 12), b) with ubiquinol (reaction 13), and c) with $O_2^-$ (reaction 10). The other two are the reactions with d) cytosolic myoglobin (reaction 14) and e) with extracellular hemoglobin (reaction 15). Some of these reactions have important biological significance. The reaction of $NO^\cdot$ with cytochrome oxidase inhibits the main pathway of $O_2$ uptake and energy production[18-23] and the reaction with ubiquinol produces ubisemiquinone that by autoxidation produces $O_2^-$ and operates as free radical initiation reaction[27].

$$NO^\cdot + Cyt\ a_3 \rightarrow Cyt\ a_3 - NO \quad [12]$$
$$NO^\cdot + UQH_2 \rightarrow UQH^\cdot + H^+ + NO^- \quad [13]$$
$$NO^\cdot + MbO_2 \rightarrow metMb + NO_3^- \quad [14]$$
$$NO^\cdot + HbO_2 \rightarrow metHb + NO_3^- \quad [15]$$

TABLE 3.– *Relative rates of reaction of nitric oxide in rat. A physiological steady state concentration of 3 x $10^{-8}$ M NO· is assumed. The steady state concentrations of the coreactants are given in each case*

| Species/[M] | Location | Reaction constant ($M^{-1}.s^{-1}$) | Reaction rate (μM/s) | Relative rate (%) |
|---|---|---|---|---|
| $O_2$-/[1.5 x $10^{-10}$] | Mitochondria | 6.7 x $10^9$ | 0.03 | 0.02 |
| Cyt $a_3$/[2 x $10^{-5}$] | Mitochondria | $10^8$ | 30 | 22 |
| $UQH_2$/[1 x $10^{-4}$] | Mitochondria | 1.2 x $10^4$ | 0.036 | 0.03 |
| $MbO_2$/[1.5 x $10^{-4}$] | Cytosol | $10^7$ | 45 | 33 |
| $HbO_2$/[2 x $10^{-4}$] | Extracellular | $10^7$ | 60 | 44 |

The reactions of NO· with $MbO_2$ and $HbO_2$ yield the met-derivatives which are subsequently reduced by the $NADPH_2$-dependent reductases and no biological effect is to be expected from a mild oxidation of the two hemoproteins. The steady state concentrations of the five biomolecules that react with NO· in rat heart under physiological conditions, the reaction constants and the expected reaction rates are given in Table 3. As it can be seen the reactions with the hemoproteins are highly favored.

## 7. Septic shock and the free radical chain reaction

It is apparent that septic shock is associated with high NO· levels in blood and tissues. It was accepted that the cytokine-dependent expression of macrophage iNOS is part of the response to septic shock and endotoxin administration. Recently, it has been found that NO· synthetized by iNOS of rat diaphragm after administration of *Escherichia coli* endotoxin participates in the development of diaphragm contractile failure[28]. The increased iNOS activity of the endotoxin treated animals increased the NO· steady state concentration in diaphragm to 0.47 μM from a level of 0.02 μM in the control animals[29]. Diaphragm mitochondria isolated from rats treated with *E. coli* endotoxin, at times similar to the ones that produce the contractile failure of diaphragm fibers, show: a) partial uncoupling and decrease in respiratory control[29], b) increase in $H_2O_2$ production[29-30], and c) nitration of mitochondrial proteins[29].

Muscle is a target organ in septic shock and for *E. coli* endotoxin. Increased spontaneous muscle chemiluminiscence is an early indicator, simultaneous with hypothermia, of the multiple dysfunction of septic shock in rats[30]. Muscle oxidative stress, as detected by in situ organ chemiluminescence, clearly precedes liver oxidative stress. Muscle dysfunction plays a key role in the circulatory and respiratory failure of septic shock.

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*Nous sommes un redoutable mélange d'acides nucléiques et de souvenirs, de désirs et de protéines. Le siècle qui termine s'est beaucoup occupé d'acides nucléiques et de protèines. Le suivant va a se concentrer sur les souvenirs et les désirs. Saura-t-il résoudre de telles questions?*

Somos una temible mezcla de ácidos nucleicos y de recuerdos, de deseos y de proteínas. El siglo que acaba se ha ocupado mucho de ácidos nucleicos y de proteínas. El que llega va a centrarse en los recuerdos y en los deseos. ¿Sabrá resolver estas cuestiones?

François Jacob

*La souris, la mouche et l'homme.* Paris: Editions Odile Jacob, 1997, p 237
(trad. *El ratón, la mosca y el hombre.* Barcelona: Crítica, 1998, p 195)