FREE-RADICAL INITIATION AND TERMINATION REACTIONS IN BIOCHEMISTRY

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The reactions that yield $O_2^{\cdot-}$ and NO are free-radical initiation reactions for biological systems. These two low molecular mass molecules with an unpaired number of electrons in *p* orbitals are able to diffuse freely, exporting a free radical reaction center from the site of formation to an eventual target. This free diffusion consideration excludes as biological free radicals to hemoproteins, ferritins and the semiquinone intermediates of the mitochondrial and endoplasmic reticulum electron transfer chains, which have unpaired electrons in *d* orbitals or highly delocalized in a *?* system. Superoxide radical is formed by collisional one-electron transfer to O_2 from semiquinone intermediates (ubisemiquinone and the flavin semiquinones of NADH-dehydrogenase and xanthine oxidase) or Fe^{2+} (hemoglobin, non-heme iron, neutrophil cytochrome b, xanthine oxidase, etc.). Mitochondrial are the most important physiological source of $O_2^{\cdot-}$, a process that accounts for 1.0-1.5 % of organ O_2 uptake. The partial reduction of O_2 also leads to the formation of H_2O_2 and $HO^{\cdot}$ as products of $O_2^{\cdot-}$ dismutation or flavoenzyme reactions and of the Fe^{2+}-catalyzed homolytic cleavage of H_2O_2. (Fenton/Haber-Weiss pathway). Nitric oxide is formed in biological systems by the well known reaction catalyzed by the family of nitric oxide synthases (NOS). The current view of the cellular distribution of NOS activity, indicates that aerobic cells have two isoenzymes, one located in the cytosolic space (iNOS, nNOS or eNOS) and other in the inner mitochondrial membrane (mtNOS). Both primary free radicals are kept in mammalian cells at steady state concentrations (0.01-0.2 nM $O_2^{\cdot-}$ and 20-200 nM NO) by termination reactions. No propagation reactions have been described for $O_2^{\cdot-}$ or NO. The most important termination reaction for $O_2^{\cdot-}$ is the superoxide dismutase (SOD) catalyzed dismutation. The enzyme, that does not have Michaelis complex or Km value, functions by alternate reduction and oxidation of the Cu^{2+} in the active center. The same mechanism is also utilized by catalase that dismutates H_2O_2 by alternate oxidation and reduction of Fe^{3+} in the hemoprotein active center. The most important termination reaction for NO is the diffusion-limited reaction with $O_2^{\cdot-}$ to produce peroxynitrite ($ONOO^-$). Nitric oxide and $ONOO^-$ constitute a biologically important metabolic route, leading, besides other pathways, to $HO^{\cdot}$ formation (Beckman-Radi-Freeman pathway). The oxidation by NO and $ONOO^-$ of ubiquinol (and other o-diphenols as adrenaline and dopamine), provides a link from the pathway dependent on NO to the one dependent on $O_2^{\cdot-}$ (Cadenas-Poderoso shunt). Hydroxyl radical and the unsaturated fatty acids of biomembranes and lipoproteins are the reactants of the O_2-dependent and well known free-radical chain reaction of lipid peroxidation.