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Free Radicals, Oxidants, and Antioxidants

GARRY R. BUETTNER* AND FREYA Q. SCHAFER
Free Radical Research Institute & ESR Facility, University of Iowa, Iowa City, Iowa 52242-1101

Free radicals are species with one or more unpaired electrons. The unpaired electron results in a species that is often highly reactive. Free radicals have a wide range of reactions; two broad classes of reactions are electron transfer and addition reactions resulting in covalent bond formation. Free radicals can be classified as reducing (donating an electron to an acceptor) or oxidizing (accepting an electron from a donor). Because of the wide range of reactivities of radicals, there is a thermodynamic hierarchy or pecking order for electron transfer reactions (Buettner, '93). Table 1 is arranged with the most oxidizing radicals at the top and most reducing at the bottom. This pecking order predicts the flow of electrons. This thermodynamic hierarchy helps to predict which species might react with each other. In general, the radical species higher in the pecking order steal electrons from the reduced species lower in the pecking order.

The pecking order predicts that peroxyl radicals will react with vitamin E (tocopherol):

$$ROO^{\bullet} + TOH \longrightarrow ROOH + TO^{\bullet}$$

$$Ascorbate + TO^{\bullet} \longrightarrow Ascorbate^{\bullet -} + TOH$$

eliminating the dangerous $ROO^{\bullet}$ and generating the much less reactive tocopheroxyl radical. This radical must be removed because it can also do damage, albeit very slowly. $TO^{\bullet}$ can be recycled by ascorbate, which is lower in the pecking order, producing the ascorbate radical that is even less reactive. Because vitamin E is located in lipid structures, this reaction also moves the radical from lipid regions into aqueous environments where enzymes can detoxify and recycle ascorbate radical back to ascorbate.

If this recycling is important, then there may be an optimum ratio of vitamins C and E to provide antioxidant protection for an organism. Gey ('98) re-examined the many epidemiological studies on vitamins C and E and found that the desirable plasma concentration of C is $\geq$ 50 μM and that of E is $\geq$ 30 μM. But most interesting was his finding that for the prevention of cardiovascular disease and cancer the desirable vitamin C/vitamin E ratio $\geq$ 1.3 - 1.5. Plasma ratios of C/E < 0.5 - 0.8 are associated with an increased risk of cardiovascular disease. This is consistent with the concept that these two antioxidant vitamins should be considered as co-antioxidants; they work together to protect organisms from deleterious free radical oxidations.

As with nutritional antioxidants, enzyme antioxidants and their cofactors must be in balance. For example, the vast majority of cancer cells have very low manganese superoxide dismutase activity when compared to their normal cell counter parts (Oberley and Buettner, '79). Increasing the amount of this enzyme in cancer cells results in them taking on normal cell characteristics (Church et al., '93). In a similar vein, decreasing glutathione, a cofactor for the glutathione peroxidase enzymes, results in a greater susceptibility to oxidative stress. Thus, balance is a key to optimal health.

TABLE 1: One-electron reduction potentials at pH 7.0 for selected radical couples

Redox Couple	$E^{o'}$/mV
$HO^{\bullet}, H^{+}/H_2O$	+ 2310
$RO^{\bullet}, H^{+}/ROH$ (aliphatic alkoxyl radical)	+ 1600
$ROO^{\bullet}, H^{+}/ROOH$ (alkyl peroxyl radical)	+ 1000
$GS^{\bullet}/GS^{-}$ (glutathione)	+ 920
$PUFA^{\bullet}, H^{+}/PUFA\text{-}H$ (*bis*-allylic-H)	+ 600
$HU^{\bullet -}, H^{+}/UH_2^{\bullet}$ (Urate)	+ 590
$TO^{\bullet}, H^{+}/TOH$ (Tocopherol)	+ 480
$H_2O_2, H^{+}/H_2O, HO^{\bullet}$	+ 320
$Ascorbate^{\bullet -}, H^{+}/Ascorbate$ monoanion	+ 282
Fe(III)EDTA/ Fe(II)EDTA	+ 120
$O_2/ O_2^{\bullet -}$	- 330
$Paraquat^{2+}/ Paraquat^{\bullet +}$	- 448
Fe(III)DFO/ Fe(II)DFO (Desferal)	- 450
$RSSR/ RSSR^{\bullet -}$ (GSH)	- 1500
H_2O/ e^{-}_{aq}	- 2870

Adapted from Buettner, '93.

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* Correspondence to : Garry R. Buettner, Free Radical Research Institute and ESR Facility, University of Iowa, Iowa City, IA 52242-1101.
E-mail: garry-buettner@uiowa.edu