MECHANISTIC AND STRUCTURAL ASPECTS OF NITROXIDES AS A MODEL FAMILY OF ANTIOXIDANTS

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Tempol (4-hydroxy-2,2,6,6-teramethyl piperidine-1-oxyl) and other stable nitroxide radicals have long been known to protect laboratory animals, bacterial and mammalian cells from the injury associated with oxidative stress conditions. The superoxide dismutase mimetic activity of nitroxides remains their most cited antioxidant mechanism although early studies have shown that they inhibit Fenton chemistry by oxidizing reduced transition metal ions, and terminate alkyl, alkoxyl and peroxyl radical chain reactions by recombination. Recent studies by us and other investigators have shown that nitroxides also react with oxidants likely to be produced under inflammatory conditions such as nitrogen dioxide, carbonate radical, and myeloperoxidase compound I and II. In parallel, we showed that catalytic amounts of tempol inhibited protein-tyrosine nitration caused by peroxynitrite/carbon dioxide or peroxidase/hydrogen peroxide/nitrite. This occurred because oxidized tempol, that is, the oxammonium cation, can be recycled back by present reductants. Based in these results, I will discuss the mechanisms by which nitroxides can combine several antioxidant properties in a single functional moiety. Also, the lessons resulting from testing tempol and analogues in experimental models of oxidative stress and inflammatory conditions will be reviewed to emphasize the need of new strategies to facilitate trafficking of nitroxides into targets that may be therapeutically relevant.