CORRESPONDENCE

How Innocuous Is Superoxide?

In "How Super is Superoxide", Sawyer and Valentine[1] set out to demonstrate that O_2^- is "innocuous". I would like to point out some of the facts they overlooked.

(1) O_2^- is stated to act as a reductant toward metal complexes. It can also act as an oxidant. Thus, Mn(II) can be oxidized to Mn(III) by O_2^-.[2,3] Mn(III) is a potent oxidant and so Mn(II) can mediate oxidations by O_2^-.[4]

(2) The statement, "However, in spite of rigorous and persistent research effort, there are no examples of O_2^- acting as an initiator of radical chain reactions", is simply wrong. O_2^- initiates the free radical chain oxidation of sulfite.[5] Indeed, the initiation of sulfite chain oxidation by the xanthine oxidase reaction was one of the earliest clues that O_2^- was produced during this enzymic reaction.[6-8] When NADH is bound to lactic dehydrogenase, it is susceptible to a free radical chain reaction which is also initiated by O_2^-.[9] Numerous autoxidations proceed by free radical chain reactions in which O_2^- can act as initiator and as chain carrier. Such autoxidations are strongly inhibited by superoxide dismutase. In this category we find the autoxidations of epinephrine,[10] pyrogallol,[11] 6-hydroxydopamine,[12] tetrahydropterins,[13] phenylhydrazine,[14] and hydroxylamine.[15]

(3) The statement that O_2^- is "innocuous" ignores a wealth of data showing that increasing the intracellular production of O_2^-, by a variety of strategies, damages and even kills cells and that elevated levels of superoxide dismutase protect.[16-21] O_2^-, generated on the surface of the hamster cheek pouch, initiates a physiological cascade resulting in leukocyte margination and vascular leakage.[22] O_2^- acts upon a macromolecular component of normal human plasma and converts it into a powerful neutrophil chemotaxin.[23]

(4) O_2^- has been seen to react with H_2O_2 to generate OH·, and this reaction is catalyzed by iron complexes, such as iron-EDTA.[24-28] Since OH· is among the most reactive chemical entities known to mankind, its production from O_2^-, under physiologically relevant conditions, makes the descriptor "innocuous" highly inappropriate for O_2^-.

(5) O_2^- has been shown to oxidize pamoic acid[29] and the (1,2-dihydroxyethyl)thiamin pyrophosphate intermediate of the transketolase reaction.[30] O_2^- causes desulfuration of thiocarbonyls,[31] attacks poly(vinyl alcohol),[32] and initiates a free radical chain oxidation in micelles containing linoleate and linoleate hydroperoxide.[33] It is clear from data already in hand that O_2^- is a major factor in the toxicity of oxygen and in the oxygen-dependent toxicities of many redox active compounds.

Irwin Fridovich

Department of Biochemistry
Duke University
Durham, North Carolina 27710

(1) Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393–400.
(2) Kono, Y.; Takahashi, M. A.; Asada, K. *Arch. Biochem. Biophys.* **1976**, *174*, 454–462.
(3) Archibald, F. S.; Fridovich, I. *J. Bacteriol.* **1981**, *145*, 442–451.
(4) Curnutte, J. T.; Karnovsky, M. L.; Babior, B. B. *J. Clin. Invest.* **1976**, *57*, 1059–1067.
(5) McCord, J. M.; Fridovich, I. *J. Biol. Chem.* **1968**, *243*, 5753–5760.
(6) Fridovich, I.; Handler, P. *J. Biol. Chem.* **1958**, *233*, 1578–1580.
(7) Fridovich, I.; Handler, P. *J. Biol. Chem.* **1960**, *235*, 1835–1838.
(8) Fridovich, I.; Handler, P. *J. Biol. Chem.* **1961**, *236*, 1836–1840.
(9) Bielski, B. H. J.; Chan, P. C. *J. Biol. Chem.* **1975**, *250*, 318–321.
(10) Misra, H. P.; Fridovich, I. *J. Biol. Chem.* **1972**, *247*, 3170–3175.
(11) Marklund, S.; Marklund, G. *Eur. J. Biochem.* **1974**, *47*, 469–474.
(12) Cohen, G.; Heikkila, R. *J. Biol. Chem.* **1974**, *249*, 2447–2452.
(13) Fisher, D. B.; Kaufman, S. *J. Biol. Chem.* **1973**, *248*, 4300–4304.
(14) Misra, H. P.; Fridovich, I. *Biochemistry* **1976**, *15*, 681–687.
(15) Kono, Y. *Arch. Biochem. Biophys.* **1978**, *186*, 189–195.
(16) Hassan, H. M.; Fridovich, I. *J. Bacteriol.* **1977**, *129*, 1574–1583.
(17) Hassan, H. M.; Fridovich, I. *J. Bacteriol.* **1977**, *130*, 805–811.
(18) Hassan, H. M.; Fridovich, I. *J. Bacteriol.* **1977**, *132*, 505–510.
(19) Hassan, H. M.; Fridovich, I. *J. Biol. Chem.* **1977**, *252*, 7667–7672.
(20) Hassan, H. M.; Fridovich, I. *J. Biol. Chem.* **1978**, *253*, 8143–8148.
(21) Hassan, H. M.; Fridovich, I. *Arch. Biochem. Biophys.* **1979**, *196*, 385–395.
(22) Del Maestro, R. F.; Thaw, H. H.; Bjork, J.; Planker, M.; Arfors, K. E. *Acta Physiol. Scand. Suppl.* **1980**, *492*, 43–57.
(23) McCord, J. M. *Agents Actions* **1980**, *10*, 522–527.
(24) Trelstad, P. L.; Lawley, K. R.; Holmes, L. B. *Nature (London)* **1981**, *289*, 310.
(25) Rosen, H.; Klebanoff, S. J. *Arch. Biochem. Biophys.* **1981**, *208*, 512–519.
(26) Fridovich, S. E.; Porter, N. A. *J. Biol. Chem.* **1981**, *256*, 260–265.
(27) Halliwell, B. *Bull. Eur. Physiopathol. Respir.* **1981**, *17*, 21–28.
(28) DiGuiseppi, J.; Fridovich, I. *Arch. Biochem. Biophys.* **1980**, *205*, 323–329.
(29) Hassan, H. M.; Dougherty, H.; Fridovich, I. *Arch. Biochem. Biophys.* **1980**, *199*, 349–354.
(30) Asami, S.; Akazawa, T. *Biochemistry* **1977**, *16*, 2201–2207.
(31) Katori, E.; Nagano, T.; Kuneida, T.; Hirobe, M. *Chem. Pharm. Bull. Tokyo* **1981**, *29*, 3075.
(32) Osawa, J.; Moriyama, C.; Nakano, H. *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 1877–1884.
(33) Sutherland, M. W.; Gebicki, J. M. *Arch. Biochem. Biophys.* **1982**, *214*, 1–11.

To the suggestion that published chemistry of superoxide was omitted from our Account,[1] we respond: (1) Superoxide certainly can oxidize metal ions and several examples are cited. (2) The observation that superoxide dismutase inhibits some autooxidation reactions does not constitute proof that superoxide is a powerful electron acceptor and highly reactive initiator of free radical reactions. Such a conclusion is as unjustified as it would be to conclude that water is a fuel because it causes acetylene to be released from calcium carbide. (3) The subject of superoxide toxicity was not addressed in our Account but has been extensively summarized elsewhere.[2] (4) The combination of hydrogen peroxide, trace metals, and ascorbic acid appears to be as lethal as hydrogen peroxide, trace metals, and superoxide.[3] Is ascorbic acid highly toxic? (5) The existence of oxidized products merely demonstrates that an oxidation has taken place, not the identity of the oxidant.

Rather than concluding that superoxide is unreactive or "innocuous", our Account describes its diverse reactions with a variety of substrates. Consideration of the 33 citations in Professor Fridovich's letter fails to disclose a single new *chemically authenticated* reaction for superoxide of a type not described in our Account. The additional reactivities for superoxide that are proposed have yet to be demonstrated in carefully controlled chemical experiments.

Donald T. Sawyer *

Department of Chemistry
University of California
Riverside, California 92521

Joan S. Valentine *

Department of Chemistry
University of California
Los Angeles, California 90024

(1) Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393–400.
(2) Fee, J. A. *Trends Biochem. Sci.* **1982**, *7*, 84–86 and references therein.
(3) Fee, J. A. In "Metal Ion Activation of Dioxygen"; Spiro, T. G., Ed.; Wiley: New York, 1980; p 209–237.

0001-4842/82/0115-0200$01.25/0