SUPEROXIDE DISMUTASE AND CATALASE AS THERAPEUTIC AGENTS FOR HUMAN DISEASES
A Critical Review

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(Received 21 July 1989; Revised and accepted 2 October 1989)

Abstract—The list of human and animal diseases for which oxygen radical scavenging therapy is being recommended continues to grow, based primarily on inferential evidence suggesting a potential role for oxygen-derived free radicals in various types of pathophysiology. Some distinct advances in pharmacologic manipulation of protein scavengers have been made which could ultimately greatly enhance the use of these reagents as drugs, as well as some innovative techniques for drug delivery (direct injection via endoscopy, iontophoresis). Unfortunately, most of the therapeutic reports in the literature, almost all of which are based on usage of standard (native) SOD and/or catalase, are still anecdotal and/or uncontrolled. A review of the human disease/treatment literature suggests that further tightening of the scientific design of such trials is still badly needed; hopefully better experimental design will be applied when products such as PEG conjugates or genetically engineered polymers are ready for testing.

Keywords—Superoxide Dismutase, Catalase, Animal models, Ischemia/reperfusion, Bronchopulmonary dysplasia, Free radicals

INTRODUCTION

The list of mammalian disease processes in which oxygen radicals are being implicated continues to grow almost as rapidly as a superoxide anion dismutates; the tabulation which I published in 19831 of nearly such 30 pathologic processes has been supplanted by new lists more than twice as long.2 This widening net of potential therapeutic usages for oxygen radical scavengers, along with new developments in the technology for mass production of human proteins, methods for manipulation of enzyme pharmacology, and identification of new classes of scavengers, has continued to fuel the search for evidence of therapeutic usefulness in human diseases. In this article, I will review the recent literature dealing with oxygen radical scavenging therapy of human disease, with mention of selected animal models of particular relevance.

I initially reviewed this subject 5 years ago in these pages,3 emphasizing at that time the arthritis literature. Since then, the greatest explosion of interest has been in the cardiovascular field, where SOD and related substances were the object of much enthusiastic research as potential modulators of ischemic damage to cardiac tissues. This area has been extensively reviewed elsewhere4-7 and cannot be covered in detail in the current paper. The initial enthusiasm for scavenging as a means of ameliorating the damage to the heart from sustained ischemia has unfortunately been tempered by realization of substantive methodologic problems and by independent observation of distinct endpoints such as arrhythmia, reversible functional defects in myocardial contractility, and infarct size.8

Some excellent general reviews of the role of oxygen derived free radicals in the pathophysiology of disease processes have been published8-10 and a superficial review of selected human therapeutic usages

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has also appeared. The discussion below will center on new developments in the pharmacology of SOD and related scavengers, as well as disease areas not reviewed elsewhere—neurologic, pulmonary, ocular, gastrointestinal, oncologic, genitourinary, etc.

In analyzing the therapeutic literature, it is important to maintain a distinction between those treatment protocols which are derived from basic principles, and those that are based exclusively on inferential evidence. One can readily do an experiment of the following type: SOD, catalase, a mixture of the two, or any other proven (or putative) radical scavenger (Table 1) is administered to an animal, added to a culture, or even given to a patient, and an event or phenomenon that had been taking place is abolished or mitigated. One then concludes that oxygen radicals were involved in the observed effects, and a self-serving rationale for therapeutic utility is devised. That’s not the same thing as invoking SOD therapy for a situation where oxygen radicals can be truly expected to play a role based on what we know about their biochemistry and pathology.

Research on the xanthine oxidase content of certain tissues, the effect of paraquat on cells, and the generation of radicals by phagocytic cells are examples of scientific data that could legitimately be invoked to support therapeutic trials of scavengers. No one to my knowledge has yet unequivocally “seen” an oxy radical in vivo. Although a number of very sophisticated indirect detection systems have been used such as spin traps and detection of specific metabolites of natural compounds, many such systems are subject to artifacts and confounding factors. A sound scientific background should precede any therapeutic attempts for human disease; pure empiric studies are much more likely to confound than clarify.

In my previous paper, I discussed the problem of an appropriate control for studies of SOD therapeutic efficacy. It was suggested that inactivated SOD (exposure to hydrogen peroxide at alkaline pH) would be an ideal control substance for the placebo arm of a study, since this would unequivocally distinguish oxygen scavenging from any other possible non-specific protein effect. Flohe has attacked this idea on the grounds that inactivated SOD “proves notoriously unstable” and that “[it] would never survive the obligatory stability testing and subchronic animal safety studies.” Although it would indeed take a great deal of time and effort to get preliminary approval to use inactive SOD in humans, this should not preclude such controls in animals studies or in vitro experiments, nor does it justify anecdotal studies with no controls at all. The stability problem to which Flohe refers apparently relates to shelf life of the inactivated material; Fridovich (personal communication) has suggested lyophilization from sucrose, and it would seem probable that given sufficient motivation, current biochemical technology should be able to design a regimen that would obviate this problem. As an alternative to uncontrolled or saline-controlled trials, the control or placebo groups could be treated with extremely low doses of the scavenger being tested, for example, conjugated SOD: it is generally accepted that a dose below 5% of the active treatment arm is equivalent to a placebo. Even albumin, readily available for human use, is a better control than saline.

Pharmacology of SOD and catalase

There are many ways to administer SOD, at least in theory (Table 2). SOD continues to be made available (in U.S. health food stores) in oral tablet form despite the florid irrationality of such a preparation. Giri and Misra prepared a labelled form of SOD by dialyzing the enzyme against EDTA and then reconstituting the apoenzyme with $^{65}$Zn$^+$: this was fed to mice by oral gavage. They traced both the fate of the metal ion and the changes in SOD enzyme activity in various tissues. Ninety percent of the label came out in the feces, and the remainder was almost certainly free metal which became separated from the protein. No discernible rise in blood or hepatic SOD activity could be demonstrated after feeding with the tablets. The medical use of SOD continues to depend on either

| Superoxide Dismutase: bovine, recombinant human | Pulmonary aerosol |
| Catalase | Intrathecal |
| Low MW SOD mimics, e.g. metal complexes | Intravenous |
| Low MW GSH peroxidase mimics, e.g. ebselen | Intra-articular |
| PEG-SOD conjugates | Intra-arterial |
| Liposome encapsulated products | IV within liposomes |
| Cationic modified proteins | Intradermal |
| SOD hinged dimers | Intralesional |
| SOD-pyran polymers | Subcutaneous |
| Combination products, e.g. SOD + Catalase | Topical: skin, eye |
| Chelators | Iontophoresis |
| Allopurinol | |
| Uric acid, ascorbate, vitamin E, etc. | |
local instillation, controlled parenteral systemic delivery, and/or development of conjugates with enhanced survival features.

The use of PEG-conjugation to lengthen the half-life of scavenging enzymes has attracted substantial attention. Mossman et al.\textsuperscript{13} administered PEG-coupled catalase to rats using an osmotic pump implanted subcutaneously for 28 days. Both lung and serum levels of catalase were found to increase in a dose-related manner without altering the normal physiology of the tissues and was not in and of itself inflammatory. Beckman et al.\textsuperscript{14} extended the PEG concept based on the ability of the polymer to induce cell fusion. Radiolabelled PEG conjugates of SOD or catalase were added to cultures of porcine endothelial cells, and enzyme activity as well as radioactivity were readily assimilated by the cells, in sufficient concentration to afford the cells protection against xanthine oxidase induced damage. The authors propose that the PEG conjugation reaction protects the proteins from the proteolysis in the medium, thereby enhancing the probability that the cells will endocytose the active agents in intact form. Since the effect (in cell culture) depends on extended time of exposure (24 h of exposure needed to attain useful levels), manipulations of SOD/catalase such as PEG conjugation would be more effective than changes which confer only proteolytic resistance without prolonging half-life. On the other hand, the rate of clearance of such conjugates by other cells (e.g., reticuloendothelial system) could also be enhanced, thereby reducing therapeutic effectiveness.

Saifer et al. have now produced PEG conjugates of bovine CuZn SOD of extremely high molecular weight (ranging from 200–100 kDa).\textsuperscript{15} Such products appear to have not only longer half-lives but also decreased potential immunogenicity. In another study utilizing PEG-catalase, Gordon\textsuperscript{16} reported that enzyme inactivated with aminotriazole retained certain anti-inflammatory effects in a guinea-pig airway irritation model even when the enzymatic activity had been abolished. This turned out to be due to contamination of the catalase with endotoxin; five different catalase preparations were found to be so contaminated. For human use, such preparations would obviously be forbidden.

A new approach to extending the half-life of SOD and catalase was reported by Schalkwijk et al.\textsuperscript{17} The proteins were made cationic, that is, isoelectric points greater than 8.5, by coupling the amino group of N,N-dimethyl-1,3-propanediamine to free carboxyl groups in the protein, a process referred to as "amidation" by the authors. The amidated proteins retained their catalytic activity, had the same molecular weight as the parent protein, had cationic IEPs, and when injected into mouse joints, were cleared much more slowly than native molecules. Amidated catalase and horse-radish peroxidase were found to have measurable anti-inflammatory effects in a mouse arthritis model, whereas amidated SOD was inactive. The cationic proteins were presumed to stick tightly to the multiple fixed anions of cartilage and other joint tissues. Although such an approach might have benefits with regard to local treatment of joint disorders, its applicability to other organs without fixed anionic charges in situ is not readily apparent.

A third new approach to SOD half-life prolongation was reported by Hallewell et al.\textsuperscript{18} using state-of-the-art techniques of molecular biology. Based on an analogy between the three dimensional structures of the native SOD dimer and the folding of immunoglobulin molecules, these authors genetically engineered a series of SOD polymers in a bacterial expression system; one consisted of two SOD single chains joined end-to-end, and the other was constructed of two SOD monomers linked by an IgA hinge sequence. Both preparations showed high specific activity of the enzyme, and the latter formed large (up to 750,000 MW) polymers which were thermostable and soluble, had well preserved enzymatic function, and showed an extended half-life in rats of 145 min. Obviously, this approach offers the most exciting (as well as the most elegant) potential for development of oxygen scavenger protein preparations for human use.

Finally, yet a fourth method of conjugating SOD has been used, viz. formation of a copolymer with pyran (divinylether maleic acid).\textsuperscript{19} The pyran (MW 5600) and SOD were reacted at pH 8.7 to form carbamide linkages and the product purified on Sephadex G-100. Modification had to be limited to 10% of the 20 free amino groups in SOD, but the resultant polymer showed a very prolonged serum half life. The product protected mice from potentially fatal influenza virus infection.

Two other aspects of SOD pharmacologic development are also of interest. Firstly, I have commented before about the disparity in both half-life and pharmacologic effect between Cu-Zn SOD and Mn-SOD.\textsuperscript{3} Nimrod et al. have prepared recombinant human Mn-SOD and have ascertained that it possesses a much longer half-life than the Cu-Zn equivalent while maintaining substantial anti-inflammatory potency.\textsuperscript{26} Secondly, Inoue et al. have experimented with several novel approaches to enhance the utility of SOD. They modified the parent protein by conjugating organic anions to the Cys residues and then complexing the product with albumin; the resultant material had a prolonged half-life with therapeutic effect and might preferentially localize to ischemic areas of low pH.\textsuperscript{21} The same group has also been trying to "target" SOD...
to potential sites of action by genetic manipulation to
incorporate heparin (or other cellular constituent) bind-
ing sites onto an SOD molecule.

Many workers in the oxygen radical field have ob-
served a synergistic inhibition of inflammatory and/or
degradative phenomena in vitro when SOD and cata-
lase are combined. This has been cited in a series of
papers from Roumania22–25 concerning a mixture of the
two enzymes (apparently 2500 units of SOD and 50,000
units of catalase per vial) which has been patented
under the trade name Epurox and which these investi-
gators are using for local therapy in a wide variety
of rheumatic, degenerative, inflammatory, and allergic
illnesses, all with “remarkable” success. No control
groups treated with alternative regimens are included
in any of their studies. Suffice it to say that the results
reported would not be acceptable for submission to the
FDA in the United States as part of a New Drug
Application.

Fortunately, the safety data for SOD continues to
be quite favorable. The agent has been administered
safely to human neonates with no evidence of local
allergic hypersensitivity, system allergy, or toxicity
towards hematologic, hepatic, or renal systems.26 In
the most recent trial of intra-articular bovine Cu-Zn
SOD treatment for osteoarthritis, the first to have been
multicenter, blinded, and randomized,27 the only drug-
related side effects were minor episodes of skin irri-
tation/itching at the injection site; the authors re-
commended that in all future trials with this agent, pre-
treatment skin testing be performed to screen out pot-
tentially allergic patients. No major toxicities have been
reported elsewhere.

Pulmonary disease and oxygen toxicity

One would naturally have expected that the toxicity
of oxygen in neonates would be one of the first human
diseases for which SOD therapy might be thought to
be beneficial, and indeed this is true. Bronchopul-
monary dysplasia (BPD) is a complication of intensive
respiratory therapy in low birth weight neonates re-
ceiving high concentrations of oxygen under pressure;
such infants are also subject to retinopathy, nervous
system hemorrhage, and bowel disorders. Under the
rationale that oxygen radicals could form in such pa-
tients and that scavenging defenses would likely be
primitive, Rosenfeld et al. conducted a randomized,
blinded trial of subcutaneous SOD in 45 neonates.28
Bovine SOD was administered every 12 h by injection,
and the subjects were monitored for both their require-
ment for continued oxygen therapy as well as the de-
velopment of clinical and/or radiologic findings of BPD.
By a variety of parameters in both groups, the SOD
trial appeared to have been most effective. Detectable
serum SOD levels were noted 2.5 hr after injection,
persisting for several hours, and no toxicity was ob-
served. Overall, the trial seemed to be quite encouraging.

Some criticisms of that study were voiced by Gerdes,29
relating to subtle interpretations of the data, well count-
ered in a reply by the original author. It is therefore
somewhat surprising that SOD treatment has not gained
greater acceptance. The major trend amongst neona-
tologists, of course, is prevention by avoidance of ex-
cessive oxygen exposure rather than drug prophylaxis
and/or treatment. The findings that oxygen radicals
can inactivate alpha-1 antitrypsin strengthens the ra-
tionale for the use of scavengers in this condition.30
since lack of anti-protease activity would enhance the
susceptibility to degradation of lung matrix constitu-
ents such as elastin. However, there are also some
obvious conceptual problems in the Rosenfeld ap-
proach. One is the disparity between their observations
of detectable circulating SOD for several hours versus
the very short half-life of SOD expected from the rat
studies. Rosenfeld points out (personal communica-
tion) that neonates have an extremely low glomerular
filtration rate and/or renal blood flow, which could
well account for this finding. Secondly, it is hard to
visualize SOD in serum effectively trapping radicals
at the level of pulmonary epithelial (or endothelial)
cell, let alone intracellularly, although SOD could be
quite effective in eliminating radicals produced by
phagocytic cells. (Both problems are addressed by the
work underway on development of SOD conjugates or
liposome delivery systems.) Finally, it might be noted
that there is a possible role for iron (and hence iron
scavengers) as a contributor to neonatal oxygen pa-
thology, based on the decreased ceruloplasmin and
transferrin levels in such patients.31

In view of the favorable findings of the 1984 Ro-
senfeld study, it is perhaps surprising that no follow
up trials have been performed. The lack of progress
has been attributed to several factors: reluctance to
continue administering bovine SOD to human neo-

nates, delay in FDA approval for recombinant human
SOD, disappointment that trials with surfactant have
not been successful, and findings that steroids may turn
on messenger for endogenous SOD, thereby obviating
the need for exogenous administration (Rosenfeld, per-
sonal communication). Once human SOD becomes
available, one would certainly anticipate that neonatal
oxygen toxicity would be a prime target of such therapy.

Two other pulmonary conditions have pathophysi-
ologic features suggesting a potential therapeutic role
for SOD. Decompression sickness, which affects di-
ers, aviators, and caisson workers, is characterized by
venous air embolism to the lungs, and superoxide
generation from PMNs has been implicated in the disorder. Disappointingly, neither SOD nor SOD plus catalase proved effective in dogs subjected to simulated diving conditions; the limitations of studies using extracellular agents to trap intracellular radicals must again be realized. The other situation involves paraquat, not normally a human toxin, except when used for a suicide attempt. Although paraquat lung toxicity starts with pulmonary edema, the usual cause of death is relentless pulmonary fibrosis leading to inability to maintain normal gas exchange. Superoxide can be implicated as an effector agent in this process, but infusion of SOD combined with high doses of ascorbic acid and vitamin E, failed to save a young woman’s life. Desperate situations call for desperate measures, but one can still argue that exogenous scavengers are unlikely to be able to get to the site where paraquat is causing free radical generation.

Central nervous system

Since hyperbaric oxygen toxicity often causes seizures prior to death, SOD was naturally tested as a potential protective agent. No beneficial effect was noted in rats pretreated with intraperitoneal SOD and then exposed to 100% oxygen at 5 atmospheres. In another study from a different group, SOD again failed, although a weak effect from catalase was noted. Since systemic administration of native proteins would not be expected to substantially enhance brain tissue levels, Yusa et al. used liposome encapsulation augment tissue levels, with a much more impressive effective. SOD delivered via liposomes also protected rats against brain edema and vascular permeability changes induced by cold injury to rat brains, a situation in which free SOD once again failed.

Oxygen toxicity is not a common cause of neurologic disease in adult humans, and so the studies mentioned above are more of pathophysiologic than therapeutic interest. With the advent of the hypotheses invoking ischemia as a cause of free radical mediated tissue damage, a new viewpoint on diseases of many organ systems, especially the CNS, becomes apparent. Using a rabbit model of ischemic damage to the spinal cord, Cuevas et al. reported a decreased incidence of paralysis and motor neuron damage when SOD was present during reperfusion. As with the cardiac studies, applicability of these findings to human disease, especially traumatic spinal cord injury, will depend on clarification of the true role of ischemia and on the ability to deliver the proper scavenger to the affected site within the time frame of maximal tissue damage, a set of obstacles not readily overcome.

Treatment of human neurologic disease with SOD has been quite limited. The study by Put exemplifies the problems in the entire field. This investigator claimed to have treated 684 patients in one year with daily or thrice weekly IM injections of catalase for a variety of ill defined syndromes characterized by cervical or lumbar pain attributed to chronic spinal disk degeneration. Although the known enzymatic action of catalase was cited in the paper, there is no known pathophysiologic justification for invoking a role for H2O2 in such disorders. Although the study was supposedly randomized, it was unblinded, a treacherous flaw when studying disorders exceedingly prone to the placebo effect of daily injections. The author concluded that IM catalase injections accelerated the recovery from these disorders.

Lund-Olesen, who by his own admittance has injected over 4000 ampules of SOD into skin, joints, spinal canal, veins, arteries, and muscles, reported non-scientifically that intrathecal SOD was beneficial for multiple sclerosis. The only scientifically valid study of SOD treatment for neurologic disease is that of Stern et al. in subjects with Duchenne’s muscular dystrophy. In this multicenter, randomized, double-blind trial, 51 patients were studied for 18 months using the best available objective criteria for that disorder. No consistent improvement in muscle strength, functional status, or biochemical markers of the disease could be proved. As usual, the treatment proved innocuous.

Noncardiac ischemia

The extensive literature on ischemia-reperfusion injury, invoking changes in xanthine oxidase/dehydrogenase content within tissues and generation of free radicals, has led primarily to treatment protocols for cardiac disease and transplant perfusion, subjects amply reviewed elsewhere. Another potential application might relate to plastic surgery, where it is often necessary to create skin flaps which must be relocated from one site to another. Sagi et al. created standardized flaps in rats, allowed them to remain ischemic for 10 h, and then reimplemented them using treatment regimens that included either perfusion with heparinized Ringer’s lactate and/or SOD. The scavenger treatment significantly enhanced and prolonged the survival of the flaps, above and beyond a mild effect seen from buffer perfusion alone. Once again, the potential for pretreatment of previously ischemic tissues with SOD before restoration of circulation gains some validity.

Another target organ of great importance with regard to human disease is the vascular supply of the intestinal tract, for example, mesenteric and splanchic arteries. Bitterman et al. produced a vascular occlusion model in rats (40 min of ischemia) such that severe
Nonvascular gastrointestinal disorders

Two anecdotal, European case report studies have been published. In an abstract, Emerit et al.,47 reported successful therapy of several cases of Crohn’s disease of the intestine or post-radiation bowel necrosis using liposome encapsulated SOD. The same author has reported an open-label, unblinded trial for Crohn’s disease, a disorder notorious for the influence of psychological factors, in which neither dosage nor route of administration nor concurrent therapy were held constant and nonobjective criteria for response were utilized.48 In a report from Romania,49 12 patients with duodenal ulcer said to be resistant to conventional therapy were treated with a hitherto unused regimen, viz. direct injection of scavenger into the tissue surrounding their ulcers via an endoscope. The product used was the aforementioned Epurox, a mixture of human SOD and catalase. As with most treatments for most diseases, the results varied: 4 patients were dramatically improved, 5 had partial relief, and three needed surgery within a few days. The authors used their results to suggest that free radicals play a role in causing the pain of ulcers. If ever there were a disease (other than arthritis) that needs carefully designed and controlled clinical trials, it is ulcer pain.

Ocular disorders

Three categories of eye disease have been treated with SOD, and all the data of which I am aware is from animals studies: canine cataract, alkali burns, and immune mediated degeneration. Although there had been some initial enthusiasm for the use of SOD in senile canine cataract, especially since SOD (as Or gotein) is well known to veterinarians, two studies involving multiple animals treated with injection into the anterior chamber of the affected eye were negative.54,55 The study by Nirankari et al.56 on alkali burns in rabbits is notable for the fact that heat inactivated SOD

Genitourinary tract disorders

The use of SOD for chronic cystitis has a long history, apparently going back to at least 1974. In a preliminary review of human treatment regimens with SOD, Beckmann and Flohe58 stated that chronic cystitis was especially amenable to SOD trials for two reasons: the ability to design controlled clinical trials, and the ease with which the active agent can be injected into the site of pathology, in this case meaning the wall of the bladder as visualized through the cystoscope. They then report uncontrolled data from 32 patients, assessed by various objective parameters but without any placebo or cross-over treatments, indicating a generally beneficial effect. Similar results were reported from Germany.51 Flohe51 contends that controlled trials would be unethical in that an effective therapy would be denied to the placebo group; crossover designs in which all subjects receive active medication at some time during the study (i.e., placebo followed by drug or vice-versa) are available which obviate this concern.

The rationale for treatment of human disease with SOD is sometimes based solely on the fact that certain disorders are resistant to all known therapies, hence SOD is offered a chance. There is no better example than Peyronie’s disease, a chronic inflammatory condition of the penis characterized by induration and fibrosis whose etiology and pathogenesis are most perplexing. Naturally, a post hoc hypothesis based on inflammatory processes can be constructed to justify such trials. SOD has been extensively used for this disorder, either by direct local injection into fibrotic plaques52 or by an innovative iontophoresis technique (using an electric current to transport the agent across the skin surface into the tissues).53 and once again, encouraging results from uncontrolled trials are reported.

shock developed. Groups of animals were treated with recombinant human SOD (Grunenthal) at the time of reperfusion. A variety of parameters were assessed (postreperfusion blood pressure, various plasma factors, survival), and the SOD treatment once again proved to be beneficial.

Only one comparable human study has been reported, from France.44 Three patients were found at surgery to have severe abdominal vascular occlusion; prior to planned surgical resection, SOD was injected intramuscularly. In all 3 cases, the authors report return of intestinal viability (normal color, peristalsis, etc.) without the need for resection. In a fourth case, an ischemic abdominal skin flap was apparently also saved. The same group reported several additional anecdotal cases with a variety of pathologies where SOD again demonstrated putative benefits.45

Shock, with or without sepsis, is often accompanied by the life threatening complication of disseminated intravascular coagulation (DIC), a syndrome characterized by extensive thrombus formation initially, followed by extensive hemorrhage due to depletion of circulating clotting factors. A model of DIC was established in rats using endotoxin infusion,56 and the potential effects of subcutaneous SOD or catalase injections were tested. At extremely high doses, both scavengers were effective in mitigating not only the changes in the coagulation proteins, but also measurable tissue damage (fibrin deposition in glomeruli).
was used for the control animals. Rabbit were subjected to a standardized corneal lesion and then treated with subconjunctival injections of native or inactivated SOD; additional animals received ascorbic acid or glutathione. Ascorbate and native SOD were both beneficial in this model.

Guy et al. sensitized guinea pigs by injection of homologous spinal cord, thereby producing an immune optic neuritis. Catalase, but not SOD, given systemically, had a mild protective effect on disk edema measured morphometrically. In a somewhat analogous model, rats were injected with an extract of normal lens combined with adjuvant, such that an inflammatory uveitis developed. Systemic treatment with SOD was reported to have lessened the severity of the inflammatory and vasculitic changes.

Miscellaneous conditions

Three rheumatologic disorders other than rheumatoid and osteoarthritis have been mentioned in the SOD therapy literature. Kawasaki disease is an acute febrile illness of children, especially prevalent in Japan, characterized by lymph node swelling, cutaneous and mucous membrane eruptions, and a high incidence of often fatal aneurysms of the coronary arteries. Treatment with liposome encapsulated SOD was reported to be of substantial benefit, even reducing the incidence of coronary artery complications. Behcet’s disease is even more mysterious, and not surprisingly, IM SOD has been tried there as well, with supposed good results, a rationale for the treatment based on increased radical generation by neutrophils from such patients has been adduced as well. Finally, even gout, the most prosaic of rheumatic diseases has been targeted for SOD therapy. (Since gout is readily treatable with conventional, nonexperimental agents, and since most gout patients are usually taking allopurinol which inhibits xanthine oxidase and/or directly traps certain radical species, the justification for testing SOD is not readily apparent.)

One rationale for using SOD therapeutically might be SOD-deficiency. If a particular tissue can be shown to be consistently low in SOD levels, then “replacement” treatment might be justified. Inconsistency in such measurements from one laboratory to the next, and from one method to the next, hampers such studies greatly. Fanconi’s anemia is one condition in which the observation has been verified. A trial with SOD produced some transient beneficial effects, albeit not sustained.

SOD has been invoked in the oncology literature in two connotations: as a potential ameliorator of the side effects of anti-cancer treatments, either radiation or chemical, and as a potential direct anti-neoplastic agent. In the former area, there have been no major new developments since Petkau reviewed the field in 1986. In the latter regard, Oberley et al., responding to the observation that SOD had no effect in rodent tumors which might have been attributed to lack of cell penetration, tested a variety of low molecular SOD mimics for antineoplastic activity; none was found.

CONCLUSION

The major developments in the SOD therapy field have been pharmacologic; documentation of clinical efficacy with the preparations already approved for use, primarily native bovine SOD, has lagged far behind. If the polymers and genetically engineered proteins can provide greater tissue penetration for longer periods with no loss of scavenging effectiveness, then greater therapeutic potential may someday be realized. The ultimate limitation, however, depends on whether or not oxygen derived free radicals actually are pathologic in human diseases, and this has yet to be proven by a means independent of what happens when scavengers are administered.

Acknowledgement—Susan A. Moak provided invaluable assistance in reviewing the literature for this manuscript.

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