Zinc and Health: Current Status and Future Directions

The Antioxidant Properties of Zinc[1,2]

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ABSTRACT The ability of zinc to retard oxidative processes has been recognized for many years. In general, the mechanism of antioxidation can be divided into acute and chronic effects. Chronic effects involve exposure of an organism to zinc on a long-term basis, resulting in induction of some other substance that is the ultimate antioxidant, such as the metallothioneins. Chronic zinc deprivation generally results in increased sensitivity to some oxidative stress. The acute effects involve two mechanisms: protection of protein sulfhydryls or reduction of ·OH formation from H_2O_2 through the antagonism of redox-active transition metals, such as iron and copper. Protection of protein sulfhydryl groups is thought to involve reduction of sulfhydryl reactivity through one of three mechanisms: (*1*) direct binding of zinc to the sulfhydryl, (*2*) steric hindrance as a result of binding to some other protein site in close proximity to the sulfhydryl group or (*3*) a conformational change from binding to some other site on the protein. Antagonism of redox-active, transition metal-catalyzed, site-specific reactions has led to the theory that zinc may be capable of reducing cellular injury that might have a component of site-specific oxidative damage, such as postischemic tissue damage. Zinc is capable of reducing postischemic injury to a variety of tissues and organs through a mechanism that might involve the antagonism of copper reactivity. Although the evidence for the antioxidant properties of zinc is compelling, the mechanisms are still unclear. Future research that probes these mechanisms could potentially develop new antioxidant functions and uses for zinc. J. Nutr. 130: 1447S—1454S, 2000.

KEY WORDS: • *zinc* • *antioxidant* • *free radicals* • *oxidants* • *trace metals*

Here, a review of the more recent literature that supports the concept that zinc is an antioxidant is presented. Historically, an antioxidant has been described as any substance that interferes with the reaction of any substance with dioxygen. The more mechanistic definition states that an antioxidant is any substance that hinders a free radical reaction (Ternay and Sorokin 1997). A free radical is any species that contains one or more unpaired electrons (Pryor 1966). It will become apparent from this review that zinc does not truly fit into either of these categories. Zinc has never been shown to interact directly with an oxidant species but rather prefers to exert its effects in an indirect manner. From a historical perspective, perhaps the earliest example of zinc as an antioxidant is its use in metallurgy. Zinc has been used for at least the past 100 y to galvanize iron or steel nails. In this process, the nail is coated either electrically or through hot-dipping with zinc, thus retarding air oxidation or rust formation. The past 20 y has seen the generation of a large amount of information on the potential role of this metal as a cellular antioxidant. Along with this information has come the inevitable explosion of commercial products seeking to take advantage of the often-anecdotal reports of beneficial effects of zinc ingestion. Here, I attempt to present information that will help to explain the antioxidant properties of zinc and support the rationale use of zinc as a pharmacologic agent under certain controlled clinical situations.

General Mechanisms

In biochemical systems, the antioxidant properties of zinc have been clearly demonstrated and, for the most part, appear to be independent of zinc metalloenzyme activity. In general, the mechanism of antioxidation can be divided into acute and chronic effects. Chronic effects involve the exposure of an organism to zinc on a long-term basis, resulting in a induction in some other substance that is the ultimate antioxidant. On the other hand, chronic zinc deprivation generally results in increased sensitivity to some oxidative stress (last reviewed in Bray and Bettger 1990), although the biochemical basis of many of these effects are not clear. The acute effects are generally thought to involve two mechanisms: protection of protein sulfhydryls or reduction in the formation of ·OH from

[1] Presented at the international workshop "Zinc and Health: Current Status and Future Directions," held at the National Institutes of Health in Bethesda, MD, on November 4–5, 1998. This workshop was organized by the Office of Dietary Supplements, NIH and cosponsored with the American Dietetic Association, the American Society for Clinical Nutrition, the Centers for Disease Control and Prevention, Department of Defense, Food and Drug Administration/Center for Food Safety and Applied Nutrition and seven Institutes, Centers and Offices of the NIH (Fogarty International Center, National Institute on Aging, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Drug Abuse, National Institute of General Medical Sciences and the Office of Research on Women's Health). Published as a supplement to *The Journal of Nutrition.* Guest editors for this publication were Michael Hambidge, University of Colorado Health Sciences Center, Denver; Robert Cousins, University of Florida, Gainesville; Rebecca Costello, Office of Dietary Supplements, NIH, Bethesda, MD; and session chair, Pam Fraker, Michigan State University, East Lansing.

[2] Supported in part by National Institutes of Health Grant HL45534 and a grant from the Heart Council of Long Island, Inc.

H_2O_2 through the antagonism of redox-active transition metals, such as iron and copper. What follows is a discussion of the more recent literature that supports these general mechanisms. The acute antioxidant effects of zinc and the effects of zinc deficiency are described in detail.

Chronic effects. The effect of the chronic administration of zinc is the clearest example of what is meant by an indirect effect. Virtually all of the beneficial effects of long-term administration of zinc can be linked to the induction of some other substance that serves as the ultimate antioxidant. In this regard, the most studied effectors are the metallothioneins. The metallothioneins are a group of low-molecular-weight (6000–7000 kDa) metal-binding proteins containing 60–68 amino acid residues, of which 25–30% are cysteine. They contain no aromatic amino acids or disulfide bonds and can bind 5–7 g zinc (mol/protein) (Bernhard et al. 1987, Kagi and Hunziker 1989, Kagi and Kojima 1987). Numerous studies have demonstrated that the chronic administration of zinc induces metallothionein in different organs such as the liver (McCormick et al. 1981), kidney (Swerdel and Cousins 1982) and intestine (Menard et al. 1981). The metallothioneins have been shown to have antioxidant effects under a variety of conditions, including radiation exposure (Matsubara 1987), toxicity from anticancer drugs such as doxorubicin (Satoh et al. 1988, Yin et al. 1998) and others (Lazo and Pitt 1995, Lazo et al. 1998), ethanol toxicity (Harris 1990) and oxidatively mediated mutagenesis (Rossman and Goncharova 1998). This list is by no means complete. Recent studies have hypothesized that the metallothioneins are a link between cellular zinc and the redox state of the cell. Under conditions of high oxidative stress, changes in the cellular redox state result in release of zinc from metallothionein as a result of sulfide/disulfide exchange (Jiang et al. 1998a, 1998b, Maret 1994, 1995). The topic of metallothioneins and zinc is discussed in detail in a subsequent review in this series.

Effects of chronic deprivation. Numerous investigators have used chronic deprivation studies in an attempt to answer the question of whether zinc has a physiological role as an antioxidant. In general, long-term deprivation of zinc renders an organism more susceptible to injury induced by a variety of oxidative stresses. Interpretation of these studies can be difficult because of the confounding problem of caloric reduction associated with zinc deprivation. It is essential that a pair-fed control group be included to differentiate between the specific effects of zinc deprivation and caloric malnutrition. By and large the best evidence for an increased susceptibility to oxidative injury comes from studies in zinc-deprived animals; these studies have demonstrated either increased free radical production or enhanced injury from exposure to an oxidative stress. Because this topic has recently been extensively reviewed, I opted to present this material in tabular form (**Table 1**).

These studies clearly show that zinc deficiency can render an animal more sensitive to an oxidative stress. However, because the mechanism of the observed effect is not clear, it is difficult on the basis of these studies to conclude that zinc is an antioxidant.

Acute effects. The acute antioxidant effects of zinc are generally manifested in the presence of a demonstrable short-term increase in levels of this metal. Basically two mechanisms have been described: sulfhydryl stabilization and reduction in the formation of ·OH from H_2O_2 and O_2^- through the antagonism of redox-active transition metals.

Sulfhydryl stabilization. One of the acute effects of zinc is an apparent stabilization of sulfhydryls, i.e., zinc protects certain enzyme sulfhydryls from oxidation. The enzyme that has been most extensively studied is δ-aminolevulinate dehydratase (EC 4.2.1.24), which catalyzes the formation of the pyrrole porphobilinogen from two molecules of δ-aminolevulinic acid. In humans, this enzyme exists as a homo-octamer of identical subunits, each with a molecular mass of ≈31,000–35,000 kDa (Anderson and Desnick 1979). δ-Aminolevulinate dehydratase are sulfhydryl dependent, and there is a strong correlation between thiol oxidation state and enzyme activity (Gibbs et al. 1985, Seehra et al. 1981). Detailed studies have shown that 8 mol of zinc is bound per 1 mol of octamer and that the amount of bound zinc closely correlates with enzyme activity. Zinc protects δ-aminolevulinate dehydratase from oxygen inactivation, preventing enzyme thiol oxidation and disulfide formation, whereas the removal of zinc increases sulfhydryl reactivity and results in the loss of enzyme activity. The protective effect of zinc was suggested to be due to maintenance of an essential sulfhydryl group (group I) secondary to decreased reactivity (Gibbs et al. 1985). Gibbs et al. (1985) suggested several possibilities to account for the stabilization of sulfhydryl groups: (*1*) direct binding of zinc to the sulfhydryl; (*2*) binding to some other protein site in close proximity to the sulfhydryl group, resulting in steric hindrance; or (*3*) binding to some other site on the protein, resulting in a conformational change, with the net result of either of these processes being a reduction in sulfhydryl group I reactivity (**Fig. 1**). There are numerous other examples of thiol-dependent enzymes and proteins containing thiol groups protected by zinc (**Table 2**) (last reviewed in Bray and Bettger 1990). Although in general, these mechanisms can be applied to any protein or peptide containing a sulfhydryl group, not all zinc-binding sulfhydryl groups can be protected from oxidation; an important example is zinc-metallothionein, in which sulfhydryl oxidation results in loss of the metal (Fliss and Menard 1992, Maret 1994).

TABLE 1

Effect of zinc deficiency on production of oxidative injury or species

Effect	Reference
↑ Hyperoxic lung damage	Taylor et al. 1988
↑ Conjugated dienes and malondialdehyde formation in liver microsomes	Sullivan et al. 1980
↑ Carbon-centered free radical production in lung microsomes	Bray et al. 1986, Kubow et al. 1986
↑ Evoked lipid peroxidation in liver microsomes and mitochondria	Burke and Fenton 1985
↑ Protein carbonyls and 8-oxo-2′-deoxy-guanosine in rat testes	Oteiza et al. 1995
↑ Sensitivity to copper-mediated lipoprotein oxidation	DiSilvestro and Blostein-Fujii 1997
↑ Galactosamine-induced hepatitis in rats	Parsons and DiSilvestro 1994

Antagonism of redox-active transition metals. Zinc has been shown in numerous systems to antagonize the catalytic properties of the redox-active transition metals iron and copper with respect to their abilities to promote formation of ·OH from H_2O_2 and superoxide. However, before presenting these studies, I would be remiss not to provide a basic review of the chemistry of the redox-active transition metals and how the formation of ·OH can promote various oxidative phenomena.

Redox-active transition metals as catalysts. Several redox-active metals, including iron and copper (Ambrosio et al. 1987, Angel et al. 1986a, 1986b, Fuller et al. 1987, Holt et al.

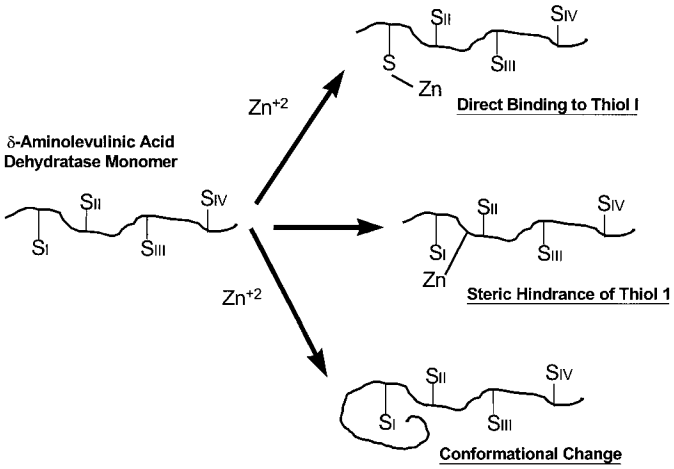
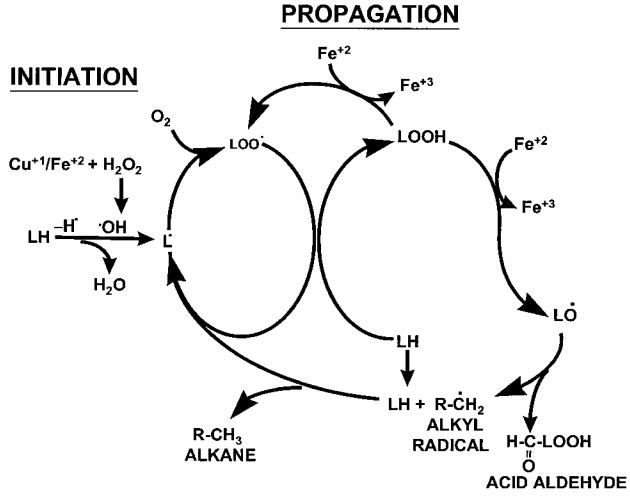


FIGURE 1 Proposed mechanisms of δ-aminolevulinic acid dehydratase sulfhydryls by zinc.



(LH = Lipid; L• = Lipid Radical; LOO• = Lipid Peroxy Radical; LOOH = Lipid Hydroperoxide; LO• = Lipid Alkoxy Radical)

FIGURE 2 Scheme of metal-catalyzed lipid peroxidation.

1986), and possibly nickel (Torreilles and Guérin 1990) and cobalt (Moorhouse et al. 1985), have been demonstrated to catalyze formation of ·OH and other radicals. There is a well known requirement for trace amounts of iron or copper to catalyze formation of ·OH from H_2O_2 and O_2^- (Chvapil et al. 1973, Czapski et al. 1984, Haber and Weiss 1934, Kohen and Chevion, 1985) through Fenton chemistry according to the following reactions.

$$2O_2^- \xrightarrow{+2H^+} H_2O_2 + O_2 \quad (1)$$

$$O_2^- + H_2O_2 \rightarrow OH^- + {}^{\cdot}OH + O_2^- \quad (2)$$

$$2AH_2 + 2O_2 \xrightarrow{(Cu/Fe)} 2A + 2H_2O_2 \quad (3)$$

$$AH_2 + 2Cu^{+2} \rightarrow A + 2Cu^{+1} + 2H^+ \quad (4)$$

$$2Cu^{+1} + 2H_2O_2 \rightarrow 2Cu^{+2} + 2\,{}^{\cdot}OH + 2OH^- \quad (5)$$

$$3AH_2 + 2O_2 \rightarrow 3A + 2H_2O + 2\,{}^{\cdot}OH\ (net) \quad (6)$$

Reaction 2 is commonly known as the Haber-Weiss reaction and is relatively slow. It has been suggested (Haber and Weiss 1934) that trace amounts of soluble iron or copper in the presence of reducing agents (AH_2), such as ascorbate, can catalyze the formation of hydroxyl radical from superoxide via the metal-catalyzed Haber-Weiss reaction (Fenton reaction) (reaction 6).

TABLE 2

Sulfhydryl-containing proteins protected by zinc

Enzyme	Reference
Dihydroorotase	Kelly et al. 1986, Washabaugh and Collins 1986
Tubulin	Hesketh 1982, Hesketh 1983
DNA zinc-binding proteins (zinc fingers)	Conte et al. 1996, Giedroc et al. 1986, Klug and Rhodes 1998
Alanyl tRNA synthetase	Wu et al. 1994
Class I tRNA synthetases	Landro and Schimmel 1993, Landro et al. 1994
5-Enolpyruvylshikimate-3-phosphate synthase	Padgette et al. 1988
E. coli DNA topoisomerase I	Tse-Dinh and Beran-Steed 1988
Protein farnesyltransferase	Fu et al. 1996
E. coli primase	Griep and Lokey 1996

Site-specific formation of radicals. Transition metals, like iron and copper, tend to undergo hydrolytic polymerization and precipitation in aqueous media at neutral pH (Spiro et al. 1967). It has been inferred that these metals can remain in solution in physiological media only by association with some high- or low-molecular-weight cellular components, such as nucleotides, peptides, polypeptides, proteins or DNA (Chevion 1988, Chvapil et al. 1973, Czapski et al. 1984). Intracellular free iron is more likely to associate with low-molecular-weight ligands, such as nucleotides, citrate, glycine and glucose (Halliwell and Gutteridge 1990), whereas copper is more likely to associate with macromolecular structures, such as DNA, carbohydrates, enzymes, peptides and proteins (Bhat and Hadi 1994, Creeth et al. 1983, Gutteridge and Halliwell 1982, Uchida and Kawakishi 1990). Once complexed at one of these sites, movement of the metal is hindered, and the association site can now serve as a locus for repetitive free radical formation through repeated redox cycling of the metal. This has become known as "site-specific" formation of radicals. Because the metal is fixed in one place, any ·OH formed, by virtue of its high reactivity, would attack adjacent structures, resulting in severe localized damage. An excellent review on the subject of site specificity can be found in Chevion (1988).

Redox-active metals and tissue oxidative injury. There is substantial evidence that metal-catalyzed formation of ·OH can initiate destructive processes. Numerous studies have demonstrated that both copper and iron play a critical role in the initiation and propagation of lipid peroxidation **(Fig. 2)**. Metal-catalyzed formation of ·OH can result in the abstraction of a hydrogen from an unsaturated fatty acid leading to lipid radical formation. This can initiate a propagative cascade of cyclical reactions, leading eventually to the repetitive formation of short-chain alkanes and lipid acid aldehydes, resulting

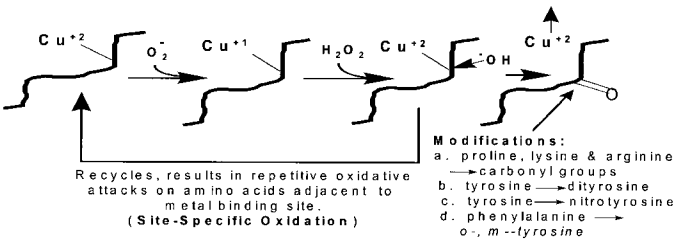


FIGURE 3 Scheme of metal-catalyzed site-specific protein oxidation.

in the destruction of lipid bilayers (Kappus 1985). Another possible site of attack can include proteins. The process of protein oxidation is initiated by the binding of a reduced redox-active transition metal to an enzyme to form a coordination complex that can then react with H_2O_2 to form ·OH (**Fig. 3**) (Fucci et al. 1983, Oliver et al. 1990, Rivett 1985, Stadtman 1990, Starke-Reed and Oliver 1989). The hydroxy radical can then abstract a hydrogen from the amino-bearing carbon, leading to the formation of a carbon-centered protein radical that undergoes a series of reactions, resulting in hydrolysis of the amino group and the formation of an aldehyde or a protein carbonyl. Once the amino group is hydrolyzed, the metal-binding site is disrupted, leading to dissociation of the metal. Because the oxidative modifications occur around the metal-binding site, the process of protein oxidation is clearly an example of site-specific reaction. An excellent review on the process of protein oxidation can be found in Stadtman (1990).

"Push versus pull." The basic assumption of the theory of site specificity is that the pool of redox-active transition metals is associated with some cellular component, thus establishing a site for the repetitive formation of ·OH. Accordingly, two potential processes that would antagonize the formation of ·OH or possibly shift the site of formation elsewhere to one less critical can be theorized. The first of these processes would be to simply remove or "pull" the metal off of its binding site through the use of high affinity chelators. The other potential means would be to force, or "push," the metal off of its binding site through the use of some chemically similar, yet redox-inactive agent. The net result would be to displace the metal into the cytosolic compartment, where it can undergo hydrolytic polymerization and precipitation as unreactive polynuclear structures (Eguchi and Saltman 1984, Spiro et al. 1967), or possibly redistribute it to some other less critical site, thus shifting the site of formation of ·OH (**Fig. 4**). By virtue of similarities in coordination chemistry (Cotton and Wilkinson 1972), it has been proposed that zinc can compete with copper or iron for certain types of binding sites. This antagonism has been most clearly demonstrated in several heme proteins where zinc can effectively compete for Cu^{+2} site-specific binding (Hegetschweiler et al. 1987, Reid et al. 1987).

Antagonism of free radical formation in chemical, biochemical and cellular systems. Perhaps the earliest report of metal antagonism in a chemical system was a study demonstrating decreases in spin-trapped ·OH from iron and cysteine in the presence of zinc, suggesting that competition between the two metals for the thiol amino acid interfered with transfer of electrons to O_2 (Searle and Tomasi 1982). In a biochemical system, the earliest report was the observation that zinc antagonized iron-mediated, xanthine/xanthine oxidase–induced peroxidation of erythrocyte membranes (Girotti et al. 1985). Since then, the antagonism has been characterized and shown to be competitive in nature. In a rather elegant study, Korbashi

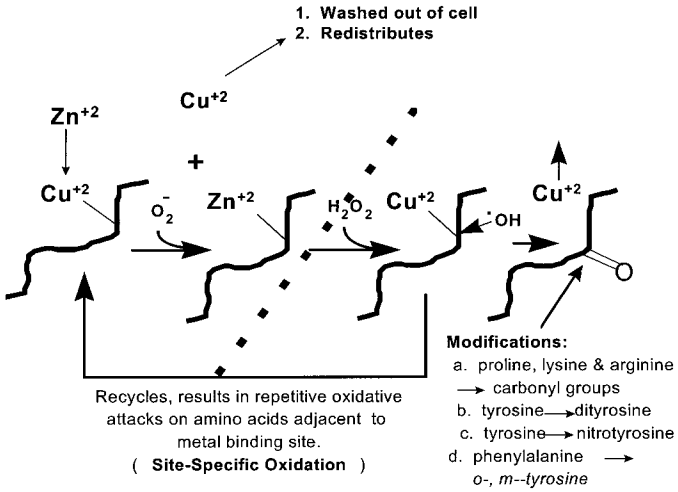


FIGURE 4 Potential mechanism for zinc as an inhibitor of site directed reactions.

et al. (1989) demonstrated that zinc-nitrilotriacetate competitively antagonized copper-nitrilotriacetate–mediated killing of *Escherichia coli* by paraquat. There have been several other studies demonstrating similar phenomenon; these are summarized in **Table 3**. It was these earlier studies that provided the rationale for subsequent studies that examined the ability of zinc to attenuate cellular injury that might have a component of site-specific oxidative injury.

Attenuation of tissue and organ oxidative injury by acute administration of zinc

The earliest reports to demonstrate possible antioxidant effects of zinc on oxidative tissue damage were related to

TABLE 3

Antagonism of free radical formation in chemical, biochemical and cellular systems by zinc

System	Reference
Biochemical	
↓ Copper- and iron/ascorbate-induced DNA breaks	Har-el and Chevion 1992
↓ O_2^-, ·OH and hypochlorite from generating systems	Bagchi et al. 1997
↓ Cu^{+2}-mediated chemiluminescence, benzoate hydroxylation and ascorbate oxidation	Lovering and Dean 1992
↓ O_2^- and ·OH from xanthine oxidase and NADPH oxidase	Afanas et al. 1995
Cellular	
↓ Phorbol ester–stimulated lactate dehydrogenase release from PC-12 cells	Bagchi et al. 1997
↓ Xanthine oxidase–mediated crosslinking of red blood cell membranes	Girotti et al. 1986
↓ O_2^- production by phorbol-12-myristate-13-acetate–stimulated leukocytes	Afanas et al. 1995
↓ Fe^{+3}-ascorbate–induced methemoglobin formation in red blood cells	Shinar et al. 1989

TABLE 4

Cardioprotective effects of zinc

Protective effect	Reference
↓ Catecholamine-induced injury	Persoon-Rothert et al. 1989, Singal et al. 1981
Ischemic injury	
↓ Reperfusion arrhythmias	Aiuto and Powell 1995, Powell et al. 1990
↑ Postischemic function	
Isolated perfused heart models (in vitro)	Powell et al. 1994, 1995
Swine cardiopulmonary bypass model (in vivo)	Powell et al. 1997

catecholamine-induced myocardial injury, a process thought to involve the production of free radical intermediates (Persoon-Rothert et al. 1989, Singal et al. 1982). In vitro and in vivo studies demonstrated that zinc has an inhibitory effect on isoproteronol-induced cardiac oxidative injury (Persoon-Rothert et al. 1989, Singal et al. 1982). Since then, we have published a series of studies describing the cardioprotective effects of zinc-bishistidinate in several in vitro and in vivo models of cardiac ischemic injury (**Table 4**). There is substantial evidence documenting the presence of various reactive oxygen intermediates in tissue, blood or perfusates from postischemic organs (Arroyo et al. 1987, Bolli et al. 1988, 1989, Das et al. 1991, Liu et al. 1990, Onodera and Ashraf 1991, Powell and Hall 1990). This topic has been the subject of many extensive reviews and is not discussed here (Bulkley 1983, Lucchesi and Mullane 1986, Parks et al. 1983, Powell 1994, Powell and Tortolani 1992, Sampson and Lucchesi 1987). Our studies were among the first to demonstrate the potential usefulness of zinc to attenuate ischemic and postischemic injury. Since then, there have been numerous studies demonstrating this property in a variety of ischemic tissues (**Table 5**). What should be apparent from this list is that investigators have tried different complexes of zinc, ranging from the simple chloride salt (Matsushita et al. 1996) to zinc complexed with protoporphyrin (Kadoya et al. 1995). Although there have been claims that one complex is superior to another, unless one can demonstrate an additional effect (chemical or therapeutic) of the complexing agent, in all likelihood it plays little if any role in the overall protective effect other than acting as a delivery vehicle. The fact remains that the one component that is common to all of these studies is the presence of the zinc. Whether any of these complexes eventually find their way into clinical usage remains to be seen but certainly should be the topic of additional studies.

Evidence of inhibition of transition metal–mediated oxidative stress. Virtually all of the evidence demonstrating that the attenuation of ischemic injury by zinc involves the inhibition of transition metal–mediated site-specific oxidative injury is derived from studies by our group. Our initial study examining the potential mechanism of zinc-mediated cardioprotection demonstrated decreased postischemic formation of $^{\cdot}OH$ when micromolar concentrations of zinc were included in the perfusate of an isolated heart (Powell et al. 1994). As part of this study, prolonged perfusion of isolated hearts with buffer containing zinc was shown to significantly decrease cardiac copper content. More recent studies (Powell et al. 1999) in the isolated perfused heart model have demonstrated that perfusion with zinc results in a significant increase in the excretion of copper from the heart, thus accounting for the decrease in myocardial tissue copper. The involvement of site-directed phenomena in this process can be inferred by the observation that zinc also decreased protein oxidation in these ischemic hearts (Powell et al. 1999). Although hesitant to imply that the complex that we use is different from all others that have been examined, the bishistidinate complex does have some unique chemical properties. With respect to copper, the formation constant of the histidinate complex of zinc is lower than that of the histidinate complex of copper (12.88 versus 18.33, respectively) (Ashmead et al. 1985). This makes it possible for a ligand exchange reaction to occur at the tissue-specific site in which zinc exchanges with loosely bound copper, which then complexes with histidine, essentially a "push-pull" phenomenon. The displaced copper can then be washed out of the cell, reducing the availability of the metal to participate in $^{\cdot}OH$ formation. The occurrence of this process is in fact suggested by the presence of increased excretion of copper from isolated hearts in the presence of zinc. The observation that improvements in postischemic function are associated with decreases in $^{\cdot}OH$ and alterations in cardiac copper content provides a reasonable basis for the theory that zinc is cardioprotective as a result of inhibition of transition metal–mediated oxidative stress.

Future directions

The production of oxidative species is a normal part of cellular respiration. Normally the cell has no difficulties with these species, is not harmed by them and may even use them to accomplish the myriad of reactions in normal metabolism. Problems only arise when the flux of oxidants becomes too great for the cellular antioxidant defense mechanisms to detoxify or when something happens to that system so it is insufficient to accomplish its normal functions. It is now apparent that oxidative injury is a component of many pathological states and that increasingly the involvement of site-directed modifications of proteins, lipids and DNA in oxida-

TABLE 5

Effect of zinc on postischemic injury

Conditions	Zinc complex	Reference
Other ischemic organs		
Stomach		
↓ Lipid peroxidation and postischemic erosion	Zinc-carnosine	Yoshikawa et al. 1992
Kidney		
↑ Postischemic function	Zinc-histidinate	Hegenauer et al. 1991
Intestine		
↓ Postischemic injury (↑ HSP 70)	Zinc-aspartate	Tons et al. 1997
Brain		
↓ Infarct size and edema formation	Zinc-protoporphyrin	Kadoya et al. 1995
↓ Nuclear damage and neuronal death	Zinc chloride	Matsushita et al. 1996
Retina		
↑ Function on electroretinography	Zinc-deferoxamine	Ophir et al. 1994
Effect of zinc deficiency		
Brain		
↑ Infarct size		He et al. 1997

tive injury is being implicated in these injurious processes. Considering the role of redox-active transition metals in these processes, one must question whether a normal function of zinc is to modulate the reactivity of these metals. Studies from our group and others have clearly demonstrated the ability of zinc to antagonize transition metal–mediated oxidations and transfer of electrons under normal and pathologic conditions. Moreover, we and others have demonstrated that zinc is capable of inhibiting the process of protein oxidation. We now know that a protein that has been oxidatively modified is an aberrant protein and is subject to rapid destruction by a variety of intracellular proteolytic systems, including, but not limited to, the ubiquitin-26S proteasome (for reviews, see Davies 1986 and Goldberg 1992). It has been proposed that one pathway to cellular injury and destruction is overactivation of these proteolytic systems. Thus, the usefulness of any substance that can interfere with the initiating steps in this process becomes clear and is worthy of further study. In light of recent studies linking proteasome activation to apoptosis mediated by caspases (for a review, see Thornberry and Lazebnik 1998), research into the ability of zinc to inhibit these processes deserves more attention, particularly since zinc has been shown to be an antiapoptotic agent (for a review, see Zalewski et al. 1991). Only by understanding the basic mechanisms by which zinc can exert its antioxidant properties will we be able to devise rational uses for this metal as an intervention not only in ischemic damage but also in other forms of oxidative injury.

ACKNOWLEDGMENT

I wish to thank Ellen Gurzenda for her assistance in the preparation of this manuscript as well as for the performance of some of the described studies.

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