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Life Extension Properties of Superoxide Dismutase Mimics Arise from "Calorie Restriction"

Crosstalk

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Manganese-salen superoxide dismutase mimics interfere with the mitochondrial electron transport chain by acting as antimetabolites and thus effect "calorie restriction," leading to extended lifespan.

Oxidative Stress, Health, and Disease

Oxidative stress results from an imbalance between the generation of reactive oxygen and nitrogen species (RONS) and their suppression by antioxidant defense mechanisms (such as the antioxidant enzymes catalase and superoxide dismutase [SOD]). This imbalance contributes to the pathogenesis of a number of inflammatory diseases including Crohn's disease, rheumatoid arthritis (RA), Alzheimer's disease, atherosclerosis, and diabetes mellitus [1]. In health, oxidative damage has been proposed as a contributor to the aging process. Recent studies have reported varying effects of antioxidant enzyme mimics on the lifespan of diverse organisms. In some studies using the nematode *C. elegans*, lifespan was dramatically extended by up to 50% after treatment with antioxidants [2]. However, repetition of this work has proved difficult [3], and in other species no such increase in lifespan was detected [4]. To add further complexity to this problem, under hyperoxic conditions treatment with Manganese (Mn)-salens shortened the lifespan of the housefly, *Musca domestica* [4]. However, in mice with inactivated mitochondrial SOD (sod2 null mice), premature death is prevented by administration of Mn-salens [5]. Although caution is needed in extrapolation of these results gleaned from such a distorted model of aging, it does add further intrigue to the scenario. Clearly, a simple approach centered on reduction of superoxide levels fails to explain these contrasting observations.

The Therapeutic Potential of Manganese-Salens

The catalytic properties of Mn-salens have been known since the beginning of the last century. Three of the most commonly known activities of Mn-salens are epoxidation and mimicry of the functions of SOD and catalase enzymes. However, since these compounds contain a redox-active metal ion capable of switching between many redox states, they are likely to participate in a much wider range of reactions. This hypothesis is supported by studies of xanthine oxidase, which contains a highly redox-active molybdenum ion. Recent studies have demonstrated that it catalyzes a wealth of new reactions pertinent to oxidative stress and beyond, including nitric oxide generation, peroxynitrite generation, and activation of the angina treatment nitroglycerin [6–8]. A full investigation of the ability of Mn-salens to catalyze these reactions is warranted prior to ascribing its life extension activity solely to removal of superoxide.

In addition to their ability to remove excess "deleterious" superoxide by mimicking the activity of SOD, Mn-salens may in fact be capable of removing radical species that are produced as a part of normal metabolic processes, and as such, they could act as antimetabolites. Consequently, at noncytotoxic concentrations Mn-salens would slow down metabolism and indirectly prevent oxidative damage. Manganese compounds have the potential to participate in a wide range of reactions in vivo, which may be either catalytic or inhibitory in nature. Lipophilic Mn(II)/(III) compounds have the ability to penetrate cell membranes and accumulate in mitochondria. Indeed, various reports show that a wide range of manganese species, including low molecular weight Mn(II)/(III) compounds, cause dysfunction of mitochondria in rats. These deleterious effects include loss of activity of Complex I, II, and III and inhibition of pyridine dinucleotide transhydrogenase [9–12]. Furthermore, Mn(II), which may be released in vivo, was specifically shown to impair the electron transport chain; in vitro experiments showed that rat mitochondria preincubated with $Mn(II)Cl_2$ exhibited a dose-dependent inhibition of electron transport [13]. This would likely correspond to inhibition of energy transduction, i.e., reduced metabolism in the animal. However, incongruent reports implicating Mn-salens in the extension of lifespan have also arisen [2–4]. One explanation for these incompatible inferences may be that the designs of the experiments are flawed by bias toward exploiting the superoxide scavenging abilities of Mn-salens rather than mitochondrial function.

To test the antimetabolite hypothesis that we propose, correlative studies should be conducted to determine the effect of Mn-salens on mitochondrial functions. It is also important to investigate the effects of non-Mn containing SOD mimics on mitochondrial activity. To this end, we have developed peptidyl mimics of SOD containing either iron(III) or copper(II) at the active site [14,15]. These "biomimetic" compounds should not exhibit the mitochondrial toxicity afforded by Mn species. At concentrations effective for SOD and catalase activities, these mimics are noncytotoxic in preliminary cell culture studies (furthermore, in a rat model of psoriasis [16] these compounds exhibit anti-inflammatory activity). With novel tools like these in hand, researchers should be able to begin to unravel the therapeutic properties of Mn-salens and perhaps prove our hypothesis by showing that these compounds do indeed extend organism lifespan by acting as antimetabolites.

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