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Review

Rationally designed mimics of antioxidant manganoenzymes: Role of structural features in the quest for catalysts with catalase and superoxide dismutase activity

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ABSTRACT

Manganese catalases (MnCAT) and superoxide dismutases (MnSOD) deplete hydrogen peroxide and superoxide in cells through a ping-pong mechanism involving cyclic oxidation and reduction of the metal cofactor. In a variety of pathological situations, the generation of reactive oxygen species overwhelms the capacity of endogenous scavengers and tissues become vulnerable to damage. Due to the limited success of the use of exogenous SOD and CAT as therapeutic agents to reduce oxidative stress damage,

Abbreviations: Adpa, bis(2-pyridylmethyl)amino-2-propionic acid; [15]aneN$_5$, 1,4,7,10,13-pentaazacyclopentadecane; baba, bis(*N*-allylbenzimidazol-2-ylmethyl)aniline; Bbzimpy, 2,6-bis(1-butyl-1H-benzo[*d*]imidazol-2-yl)pyridine; BIG, *N*,*N*-bis[(1-methyl-2-imidazolyl)methyl]glycinate; Bimtacn, 1,4-bis(benzimidazol-2-ylmethyl)-1,4,7-triazacyclononane; BimindH, 1,3-bis(2′-benzimidazolylimino)isoindoline; BMPG, *N*,*N*-bis[(6-methyl-2-pyridyl)methyl]glycinate; BSA, bovine serum albumin; 2-(CH$_2$)$_2$OHpy, 2-hydroxyethylpyridine; 2-CH$_2$OHpy, 2-hydroxymethylpyridine; CDL, 6^A-deoxy-6^A[(*S*-cysteamidobenzoyl(3,4-diamino)-*N*,*N*′-bis(salicylidene))]-β-cyclodextrin; CM-PVIm, carboxymethylpoly(1-vinylimidazole); Cy[15]aneN$_5$, 2,3,8,9-bis-cyclohexano-1,4,7,10,13-pentaazacyclopentadecane; CySalen, *N*,*N*′-bis(salicylidene)-1,2-diaminocyclohexane; CySalenSO$_3$, *N*,*N*′-bis(5-sulfonatosalicylidene)-(*R*,*R*)-1,2-diaminocyclohexane; Csalophen, *N*,*N*′-bis(salicylidene)-3,4-diaminobenzoic acid; Etobb, 1,3-bis(1-ethylbenzimidazol-2-yl)-2-oxopropane; EUK-108, [Mn(III)salen(OAc)]; EUK-113, [Mn(III)(3-OMe-salen)(OAc)]; EUK-172, [Mn(III)(salophen)(OAc)]; EUK-207, Mn(III) complex of a cyclic salen-crown ether; Hbpg, bis-2-picolylglycylamine; H$_2$dapsox, 2,6-diacetylpyridinebis(semioxamazide); H$_2$Daphp, 2,6-bis((2-(pyridin-2-yl)hydrazono)ethyl)pyridine; H$_2$Dcphp, *N*′^{2}, *N*′^{6}-di(pyridin-2-yl)pyridine-2,6-dicarbohydrazide; HEPES, 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid; H$_3$L6, 1-[*N*-(2-pyridylmethyl),*N*-(2-hydroxybenzyl)amino]-3-[*N*′-(2-hydroxybenzyl),*N*′-(4-methylbenzyl)amino]propan-2-ol; HL12, 2-{[[di(2-pyridyl)methyl](methyl)amino]methyl}phenol; HL13, Bis(pyrazol-1-yl)acetic acid; HPBMPA, *N*-propanoate-*N*,*N*-bis-(2-pyridylmethyl)amine; HPClNOL, 1-[bis(pyridin-2-ylmethyl)amino]-3-chloropropan-2-ol; H$_2$pda, 2-picolyldiglycylamine; Hptp1, *N*-(2-hydroxy-5-methylbenzyl)-*N*,*N*′,*N*′-tris(2-pyridinylmethyl)-1,2-ethanediamine; H$_2$qtp1, *N*-(2,5-dihydroxybenzyl)-*N*,*N*′,*N*′-tris(2-pyridinylmethyl)-1,2-ethanediamine; H$_2$pyr$_2$en, 1,2-bis(pyridoxylidenamino)ethane; H$_2$pyr$_2$pn, 1,3-bis(pyridoxylidenamino)propane; HSA, human serum albumin; HSJ-0017, manganese(III) 5,10,15,20-tetrakis[3-(2-(2-methoxy)-ethoxy)ethoxy]phenyl porphyrin chloride; HSM, hollow silica microspheres; HSX-salophOMe, Hangman salophen xanthene ligand; HSX, ^{t}Bu-Cysalen, Hangman salen xanthene ligand; Imtacn, 1-(benzimidazol-2-ylmethyl)-1,4,7-triazacyclononane; IndH, 1,3-bis(2′-pyridylimino)isoindoline; IPG, *N*-[(1-methyl-2-imidazolyl)methyl]-*N*-(2-pyridylmethyl)glycinate; L1, [*N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*,*N*-di(2-pyridylmethyl)]amine; L2H, 2-(benzyl(2-(bis(pyridin-2-ylmethyl)amino)ethyl)amino)acetic acid; L3, *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)ethane-1,2-diamine; L4H, *N*-(2-hydroxybenzyl)-*N*,*N*′-bis[2-(N-methylimidazolyl)methyl]ethane-1,2-diamine; L5, *N*-methyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)ethane-1,2-diamine; L7, pyridine pentaazamacrocyclic ligand with acid/base auxiliary; L8–10, Me$_2$-pyane functionalized with alkyl ether chains: C$_{12}$H$_{25}$ (L8), C$_{16}$H$_{33}$ (L9), C$_{22}$H$_{45}$ (L10); L11, 4,10-dimethyl-1,4,7,10-tetraazacyclododecane-1,7-diacetate; M40401, manganese(II)dichlorido{2*S*,21*S*-dimethyl-(4*R*,9*R*,14*R*,19*R*)-3,10,13,20,26-pentaazatetracyclo[20.3.1.0^{4,9}0^{14,19}]hexacosa-1(26),22(23),24-triene}; M40403, manganese(II)dichlorido{(4*R*,9*R*,14*R*,19*R*)-3,10,13,20,26-pentaazatetracyclo[20.3.1.0^{4,9}0^{14,19}]hexacosa-1(26),-22(23),24-triene}; M40404, manganese(II)dichlorido{2*R*,21*R*-dimethyl-(4*R*,9*R*,14*R*,19*R*)-3,10,13,20,26-pentaazatetracyclo[20.3.1.0^{4,9}0^{14,19}]hexacosa-1(26),22(23),24-triene}; 4′MeIndH, 1,3-bis(4′-methyl-2′-pyridylimino)isoindoline; Me-PhimpH, 2-(1-(2-phenyl-2-(pyridine-2-yl)hydrazono)ethyl)phenol; Me$_2$EBC, 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane; Me$_2$-Pyane, Me$_2$[15]pyridinaneN$_5$, *trans*-2,13-dimethyl-3,6,9,12,18-pentaazabicyclo [12.3.1]octadeca-1(18),14,16-triene; Me$_2$-Pyene, 2,13-dimethyl-3,6,9,12,18-pentaazabicyclo[12.3.1]-octadeca-1(18),2,12,14,16-pentaene; MPBMPA, methyl 3-[bis(2-pyridylmethyl)amino]propanoate; MnPD, 1,3-di[5-(*N*-methylene-pyridinium-4-yl)-10,15,20-triphenylporphynato manganese(III)]; M4PyP$_3$P, 5-(*N*-methylpyridinium-4-yl)-10,15,20-triphenyl porphyrin; N4py, *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine; naphtophen, 1,2-bis((2-hydroxynaphthalen-1-yl)methyleneamino)benzene; naphpn, 1,3-bis((2-hydroxynaphthalen-1-yl)methyleneamino)propane; NBT, nitrobluetetrazolium; N-PhimpH, 2-((2-phenyl-2-(pyridin-2-yl)hydrazono)methyl)napthalen-1-ol; P^1, [Mn(III)-*meso*-tri(*N*-methylpyridinium-4-yl)mono(4-carboxyphenyl)porphyrin]; P^2, [Mn(III)-*meso*-tri(*N*-methylpyridinium-4-yl)mono(*N*-4-carboxybenzyl-4-pyridyl)porphyrin]; PBMPA, 3-[bis(2-pyridylmethyl)amino]propanoate; PEG, polyethyleneglycol; PhIH, 4-(2-salicylamino-ethyl)-imidazole; PhimpH, 2-((2-phenyl-2-(pyridin-2-yl)hydazono)methyl)phenol; Pi, inorganic phosphate; PI$^-$, 2-{[(1-methyl-2-imidazolyl)methyl]amino}phenolate; Pimp, pyridine-2,6-bis(carbaldehydeimine-2-hydroxyphenyl); Pyane, pyridine[15]aneN$_5$, 3,6,9,12,18-pentaazabicyclo[12.3.1]octadeca-1(18),14,16-triene; Py$_2$N$_2$, 2,11-diaza-[3,3](2,6)pyridinophane; S-1, (*1S*,*2S*)-*N*,*N*′-bis-[3-*tert*-butyl-5-chloromethyl-salicylidine]-1,2-cyclohexanediamine; S1m, chiral macrocyclic salen ligand; SalbutOH, 1,4-bis(salicylidenamino)butan-2-ol; Salen, 1,2-bis(salicylidenamino)ethane; Salophen, *N*,*N*′-bis(salicyliden)-1,2-phenylendiamine; Salpn, 1,3-bis(salicylidenamino)propane; SalpnOH, 1,3-bis(salicylidenamino)propan-2-ol; SL, aza-scorpiand like macrocycles; S$_2$Py$_3$, 2,6-bis[((2-pyridylmethyl)thio)methyl]pyridine; TBAP, 5,10,15,20-tetrakis(4-benzoate)porphyrin; TDMImP, 5,10,15,20-tetrakis-(1,3-dimethylimidazolium-2-yl)porphyrin; TE-2-PyP, 5,10,15,20-tetrakis(*N*-ethyl-2-pyridyl)porphyrin; TECP, 5,10,15,20-tetrakis-(ethoxycarbonyl)porphyrin; TM-2-PyP, 5,10,15,20-tetrakis(*N*-methyl-2-pyridyl)porphyrin; TM-3-PyP, 5,10,15,20-tetrakis(*N*-methyl-3-pyridyl)porphyrin; TM-4-PyP, 5,10,15,20-tetrakis-(*N*-methyl-4-pyridyl)porphyrin; TMIMA, tris[(1-methyl-2-imidazolyl)methyl]amine; TnBuOE-2-PyP, 5,10,15,20-tetrakis(*N*-(2′-n-butoxyethyl)pyridinium-2-yl)porphyrin; TnHex-3-PyP, 5,10,15,20-tetrakis(*N*-hexyl-3-pyridyl)porphyrin.

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investigations have been directed to the design of low molecular-weight antioxidant catalysts (SOD- or CAT-mimics). To disproportionate superoxide and hydrogen peroxide efficiently, the reduction potential of MnSOD and MnCAT is fine-tuned to values much lower than that of the $Mn^{3+}(aq)/Mn^{2+}(aq)$ couple. In the artificial catalysts, the number and type of ligands, the local charge, the geometry around the metal, are among the factors that introduce a way of tuning the redox potential of Mn to face redox reactions. However structural and electronic factors affecting SOD activity do not parallel those controlling CAT activity. This review focus on synthetic mononuclear Mn complexes with SOD and/or CAT activity, stressing the role of ligand donor sites, endogenous acid/base groups, metal environment and second-sphere effects in the catalytic activity.

Contents

1. Introduction

Molecular oxygen is indispensable to the life on this planet and essential for efficient aerobic metabolism where the four electron reduction of O_2 to water constitutes the terminal reaction of the aerobic respiratory chain. However, during normal cellular metabolism, O_2 can be converted to the superoxide radical anion ($O_2^{\cdot-}$), a deleterious reduction intermediate species which is the primary source for other reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) and hydroxyl radical ($HO^{\cdot}$). These powerful oxidants can attack tissues, membranes and their proteic environment, thereby turning into lethal agents against cell structure and functioning. *In vivo* protection occurs via suppression of the ROS cytotoxins through a cascade of dismutation processes. These reactions are mediated by two key classes of metalloenzymes: superoxide dismutases (SODs) and catalases (CATs). Dismutation of $O_2^{\cdot-}$ leads to O_2 and H_2O_2 either spontaneously or through the enzymatic processes catalyzed by SODs [1]. As a consequence, wherever $O_2^{\cdot-}$ is generated, H_2O_2 is also formed. H_2O_2 is stable at biological pH, easily crosses lipid membranes [2] and can readily react with reduced transition metal ions to generate the highly reactive $HO^{\cdot}$ by Fenton-like reactions [3]. Accordingly, full detoxification of $O_2^{\cdot-}$ may not be achieved by SOD alone, but only when it is coupled to CAT, the enzyme that catalyzes the disproportionation of H_2O_2 to molecular oxygen and water [4]. In a variety of pathological situations, ROS generation overwhelms the capacity of endogenous scavengers to neutralize them and tissues become vulnerable to damage. Exogenous SOD and CAT have been used as therapeutic agents to reduce oxidative stress damage [5], although with limited success [6]. The major limitations associated with the therapeutic applications of these enzymes are their large size, solution instability, short half-lives, antigenicity and high-manufacturing costs [7]. To overcome these limitations, investigations have been directed to the design of low molecular-weight antioxidant catalysts (SOD- or CAT-mimics) [8]. These catalytic ROS scavengers would be clinically superior to stoichiometric ones [9] and should have better bioavailability than exogenously administered antioxidant enzymes. Among them, manganese based mimics are the most widely investigated, mainly because of its low toxicity (Mn is not prone to generate $HO^{\cdot}$ in Fenton type reactions) compared, for instance, to iron or copper in the case that free metal is released from the catalyst [10]. Most of these manganese-based catalytic antioxidants have been tested as decomposition catalysts for $O_2^{\cdot-}$. However, since catalase activity would be a key attribute for synthetic ROS scavenging compounds, some efforts have focused on development of catalysts with dual SOD/CAT activity for possible therapeutic use. This review focus on advances on synthetic Mn complexes with SOD and/or CAT activity that can be used as artificial small molecule catalysts for ROS detoxification, with emphasis on the role of redox potentials, coordination geometry and ligands donor sites in the mimicking activity. Our purpose is to compare structural and electronic properties of manganese complexes with SOD, CAT or dual SOD/CAT activity and analyze how these features modulate their reactivity.