SOD MIMICKING PROPERTIES OF COPPER (II) COMPLEXES: HEALTH SIDE EFFECTS

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Controlled regulation of the superoxide ion in living systems is an important challenge, due to the multiple pathological involvements of this radical ion.

Among the three naturally occurring superoxide dismutases (SODs) the copper zinc SOD has been extensively investigated, with as a consequence a good knowledge of its structure and behaviour.

I. Mechanism of \( \text{O}_2 \) dismutation by Cu Zn SOD

The dismutation proceeds in two steps at the level of the copper ion:

\[
\text{Protein-} \text{Cu}^{2+} + \text{O}_2 \rightleftharpoons \text{Protein-} \text{Cu}^+ + \text{O}_2
\]

In this first step the superoxide binds probably to the copper ion in axial position, the subsequent reaction being an inner sphere electron transfer.

\[
\text{Protein-} \text{Cu}^+ + \text{O}_2 + 2 \text{H}^+ \rightarrow \text{Protein-} \text{Cu}^{2+} + \text{H}_2\text{O}_2
\]

SOD is generally associated with a catalase, their partnership constituting a reciprocally protective set. Indeed SOD is inhibited by \( \text{H}_2\text{O}_2 \), catalase is inhibited by \( \text{O}_2 \).

\( \text{Zn}^{2+} \) plays at least a structural part in this system.

The SOD molecule is a dimer with a molecular weight of 31,500, it is composed of two sub units, each containing a \( \text{Cu}^{2+} \) and a \( \text{Zn}^{2+} \) ion. In each unit these ions are separated by an imidazole ring (fig.1), the distance between them being 0.6 nm.
Coordination structures of the metal ions are slightly distorted for the tetrahedrally coordinated Zn, but more deeply altered for the square planar Cu. An exchangeable water molecule is set in axial position on Cu$^{2+}$. The copper ion inside the enzyme is strongly coordinated and directly accessible to O$_2$ and solvent. The eight histidines in each subunit are equally accessible to solvent molecules.

Research on Cu Zn SOD models (1,2,3,4) give some mechanistic information on the dynamics of substrate interactions with copper ions in the enzyme. The superoxide ion would be steered along a channel in the apoenzyme to the Cu$^{2+}$ ion, in a non centrosymmetrical electric field due to the electric charge distribution in the polypeptidic structure. The positive charges on the lysine and histidine would play an important role in this driving effect, which would increase the diffusion controlled rate by about 40%.

There is yet some incertitude as to the origin of the proton in the second step of the dismutation.

II. SOD Mimics

Natural SOD is rather a large molecule. Its diffusibility through most of the living tissues is low and it is almost negligible through cellular membranes. In view of therapeutical uses, in which a higher ability of migration through tissues and a capacity of intracellular transference (e.g. in post-radiolysis treatments) are required, it would be advisable to get low molecular weight SOD mimics available. Such enzymatic systems should reach deeper and faster their targets. Moreover in some uses a reduced SOD activity or an increased stability could be required.

From a scientific stand point, specially designed SODs would constitute tools of value in the investigation of a field of entangled reactions. Among these the problem of a possible partnership between SOD and interleukines appears as an interesting one.